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OF
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THREE INSTANCES OF UNUSUAL GONOCOCCAL INFECTION[1]

BENJAMIN M. BAKER, JR., M.D.

AND

EDWARD P. CARTER, M.D.

From the Cardiographic Laboratory of the Johns Hopkins University and Hospital

Grave consequences following gonococcal infections are relatively infrequent. That they may and do occur, giving rise to serious and even fatal illness, involving one or other of the serous surfaces and in some instances leading to localized abscess formation, is well known. It is, however, surprising that a disease so widespread as acute gonococcal infection should lead so seldom to a fatal septicaemia. Referring to this subject Osler (4) states that there were but 665 fatal cases of gonococcal infection in the United States Registration Area in 1920. Seven years later in 1927,[2] with a greatly increased population, there were only 1026 deaths attributed to gonococcal infections in this area, which includes 42 states and the District of Columbia (11). At best these figures are of only approximate value. The difficulty of cultivating the organism from the blood-stream during life accounts for the failure to separate certain cases of gonococcal septicaemia from other obscure fevers.

For some unexplained reason, during the last few years, a considerably larger number of cases than formerly of acute general infections, presumably due to the gonococcus, have been observed in the wards of the Johns Hopkins Hospital. Three of these were of such unusual interest as to justify, we believe, a detailed clinical and anatomical description, together with a brief discussion of certain important features.

Case I. Septicaemia. C. J., *aet.* 25, Unit 9896, a colored housewife, admitted December 9, 1928 and died January 8, 1929.

History. A family and past history could not be obtained because of the mental

[1] Submitted for publication December 1, 1931.

[2] These are the latest complete figures available.

condition of the patient, and ignorant friends and relatives could contribute nothing of value. On December 2, 1928, she was admitted to the obstetrical service and four days later was delivered of a full-term child who died after four days of hemorrhagic disease. A week before entry she had begun to complain of a pain in the left shoulder which was followed on the following day by a severe rigor, exaggeration of the pain in her shoulder and the development of similar pains in the other shoulder, both wrists, ankles and temporo-mandibular joints. There was daily fever with sweats and on the day before admission the patient complained of sore throat. On entry the only physical findings of note centered in the joints. Both ankles and knees, the right wrist, elbow and shoulder joint and both temporo-mandibular joints, though not swollen, were extremely painful and tender on pressure and movement. A smear from the uterine cervix showed many gram-negative intracellular diplococci. The Wassermann test was negative. The course of the temperature, pulse rate, blood examinations and the results of cultures from the blood are recorded in chart 1.

Two days after delivery she developed a severe angina with laryngitis; the temperature, previously kept in check by massive doses of sodium salicylate, rose, the patient seemed much worse and was transferred to the medical service.

Physical examination. On admission she appeared very ill, was apathetic and apparently in great pain. Temperature 100.6°, pulse 120, respirations 24, blood pressure 145/70. The voice was hoarse, and over the pharynx there was a rough membrane, extending down over the posterior pillars, uvula and tonsils. The pupils reacted to light, and ophthalmological examination revealed normal fundi. The lymph nodes were not significantly enlarged. Both wrist joints and the left shoulder and knee joints were painful on motion; they were tender and there was moderate peri-articular swelling without apparent effusion into the joints. The heart was not enlarged; the sounds were clear and there were no murmurs. The lungs showed nothing remarkable on percussion or auscultation. The abdomen was soft, and the liver and spleen were not felt.

Blood. R. B. C. 2,310,000. Hb. 60 per cent. W. B. C. 19,600 with 83 per cent polymorphonuclear leukocytes. The urine of high specific gravity contained considerable albumin, many hyaline and a few granular casts but no red blood cells.

Cultures from the throat showed numerous haemolytic streptococci, but no diphtheria bacilli. The Wassermann test was negative. Repeated blood cultures with various techniques showed no growth.

Course of the disease. As can be seen from chart 1, the temperature rose rapidly, and throughout the period of observation was constantly elevated and accompanied by a conspicuous tachycardia. Delirium and hallucinations set in, and the joints continued to cause great distress in spite of massive doses of sodium salicylate. The right knee was tapped and a small quantity of greenish purulent fluid was removed, which clotted on standing and contained 1700 polymorphonuclear leukocytes per c.mm. On culture no growth was obtained, but in stained smears a few gram-negative diplococci were observed.

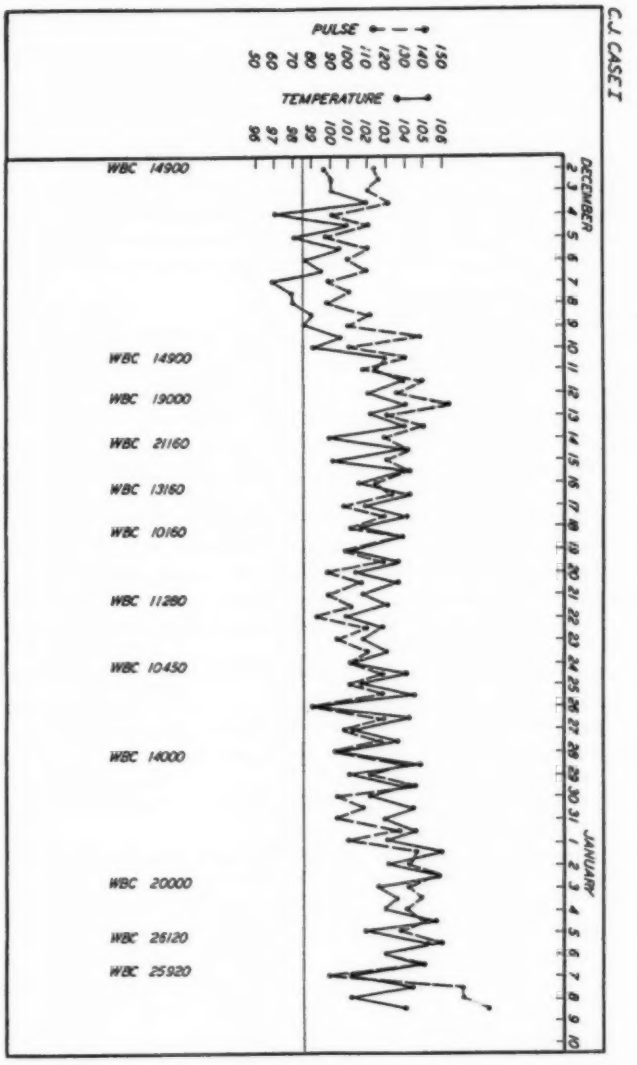

CHART 1. CASE 1, C. J., SHOWING DAILY VARIATIONS IN TEMPERATURE, PULSE RATE AND WHITE BLOOD COUNTS

The picture of profound intoxication progressed, and a leukocytosis ranging between 10,000 and 26,000 accompanied the high fever. There was strikingly little change in the physical findings, and except for a soft systolic murmur at the apex and in the pulmonary area, the auscultatory findings over the heart were not remarkable, and there was never definite evidence of valvular disease. The progress was steadily down hill; extensive bed sores developed over the back. Evidences of terminal pneumonia appeared at both bases posteriorly; the patient became more and more intoxicated, finally comatose and died. Repeated examinations of the urine revealed constantly traces of albumin and a few hyaline and granular casts and leukocytes but never red blood cells. An intracutaneous tuberculin test, 0.01 mg., was negative, and the spinal fluid withdrawn two days before death was not abnormal.

Autopsy 10734. January 10, 1929.

Anatomical diagnosis. Gonococcal arthritis; abscess containing gonococci between the costal cartilages. Acute splenic tumor; punctate hemorrhages in kidneys; hemorrhagic cystitis; anemia; old pleural adhesions. Thrombosis of veins of broad ligaments. Lobular pneumonia.

The body was that of a fairly well built, poorly nourished, colored woman. There was localised swelling over the flexor surfaces of the wrists and more marked swelling on the extensor surfaces of the hands. Overlying and extending into the perichondrium of the cartilage of the anterior surface of the left 7th rib and about 2 cm. from its junction with the sternum was an abscess about 1 cm. in diameter containing thick pus, smears from which showed countless gram-negative intracellular diplococci. The heart weighed 320 gm. and the muscle was soft and flabby. All of the valves were quite delicate and no vegetations could be seen. The aorta was smooth and elastic.

There was no fluid in either pleural cavity but there were small fibrous adhesions between the lung and diaphragm on both sides. Both lungs appeared to be air-containing throughout, but on section in the lower lobes there were a few small reddish firm areas which appeared to be due to consolidation. The spleen weighed 115 gm. and was firm and grayish red.

The liver, adrenals, kidneys, gastro-intestinal tract, pancreas, ovaries, uterus, neck organs and brain were quite normal.

Microscopical notes. A section through the distal end of the left ulna showed normal cartilage but just underneath it a number of areas infiltrated with leukocytes and mononuclear wandering cells. Sections through the abscess over the sternum showed a cavity lying chiefly in the connective tissue over the cartilage. It was filled with leukocytes and mononuclear wandering cells and lined with granulation tissue imbedded in which were numerous leukocytes containing diplococci with the morphological appearance of gonococci. In the parenchyma of the lungs were many small areas of fresh pneumonia.

The right kidney showed many small scars beneath the capsule. The glomeruli, although in some regions rather dense and cellular, contained no hemorrhages or adhesions. Several swollen tubules contained blood. The veins of the broad

ligament were filled with thrombi partly hyalinized. The epithelium over a great part of the surface of the bladder was missing and the subjacent tissues were heavily infiltrated with lymphocytes, plasma cells and large mononuclear cells. The heart, spleen, liver, adrenals, pancreas, and brain showed no noteworthy abnormalities.

Discussion

This case was one of absorbing interest throughout the period of clinical observation and gave rise to heated discussion as to the proper diagnosis. The disease began as an acute polyarthritis which was accompanied by an endocervicitis from which organisms, presumably gonococci, were demonstrated in smears. Similar organisms were seen in smears from purulent material aspirated from one of the affected joints. As the disease progressed, all the signs of a grave infection with delirium, high fever, tachycardia, emaciation, severe anemia and pronounced leukocytosis presented themselves. In the face of a picture, apparently the result of a general blood-stream infection and the failure to cultivate any organism from the blood after repeated attempts, the diagnosis of gonococcal septicaemia was strongly suspected. Pneumonia was obviously a terminal event. In spite of the failure to cultivate and to identify with accuracy any offending organism even before or after death, it seems justifiable to conclude that the clinical impression was a correct one.

Case II. Acute aortic endocarditis. O. J., S., negro laborer, *aet.* 54, Unit 20462, was admitted September 6, 1928, and died October 29, 1928.

History. He complained of jaundice. His family history revealed nothing of note. In the past, he had enjoyed excellent health, and had worked hard throughout his life without knowledge of any physical disability. At the age of 14, there had been pain in the right arm which his physician pronounced inflammatory rheumatism, but so far as he knew this was not accompanied by any complication. At the age of 19 he had a chancre and a Neisserian infection, and during 19 years he had taken a course of six intravenous injections every five or six years.

For two and a half years before his admission to the hospital he had known that his blood pressure was high, but the only symptoms of note accompanying it were occasional headaches of moderate severity and short attacks of vertigo. Four months before admission he noted a fullness in the epigastrium, and slight nausea without vomiting, particularly after meals. Two months before admission, he became aware of jaundice; itching of the skin soon set in and he lost 22 pounds in weight.

Physical examination. Temp. 98.6°F., Pulse 80, Resp. 20, B. P. 200/116. There was deep jaundice, and he appeared to have lost a considerable amount of weight. The peripheral arteries were tortuous and thickened and there was advanced arcus senilis. An examination of the ocular fundi revealed well advanced arteriolosclerosis without exudates or haemorrhages. The peripheral lymph nodes were easily palpable, but not remarkably enlarged. The percussion note throughout the lungs was normally resonant, the breath sounds were vesicular and no râles were heard. *Heart:* The apical impulse was quite forceful; the cardiac dulness extended 4.5 cm. in the 4th i.s. and the retromanubrial dulness was 5 cm. in the 2nd i.s. The sounds were everywhere loud and clear. The aortic second sound was accentuated, but not tympanitic, and a soft, rather low-pitched systolic murmur was heard over the body of the heart. No diastolic murmur was heard. The liver was enlarged and extended 5 cm. below the costal margin, and was irregular in contour. Several observers felt a nodular mass about the size of a lemon under the margin of the liver in the right upper quadrant.

Blood: Hb. 75 per cent. R. B. C. 3,800,000. W. B. C. 7,750. The differential formula was not remarkable. The urine, which was concentrated, showed a trace of albumin and a few hyaline casts in the sediment. The Wassermann test was negative. The Van den Bergh test gave a direct reaction of 39 mg. per cent. The stools contained no urobilin and the urine contained bilirubin and bile salts.

A diagnosis of carcinoma of the head of the pancreas was made, and on the 28th of September, 1928, he was transferred to the Surgical Service for an exploratory laparotomy. A much enlarged gall-bladder with a large mass in the head of the pancreas and multiple, small metastases in the liver were found. An anastomosis was made between the gall-bladder and the stomach, and the jaundice lessened considerably so that he felt somewhat more comfortable. The day after operation, fever, which was absent before, appeared and for the remaining 14 days of his stay on the Surgical Service the temperature ranged between 99° and 101.5°F. The patient did not rally well from the operation; there was almost complete anorexia and he seemed listless and generally weaker. He was transferred back to the Medical Service, October 12, 1928. Temperature 102°F. Pulse 88. Resp. 20 B. P. 160/110.

There was no remarkable change in the physical findings. The same systolic murmur noted on admission over the body of the heart persisted, but no diastolic murmur could be heard. The anemia had progressed somewhat; Hb. 50 per cent. R. B. C. 2,160,000. W. B. C. 10,440 with 86 per cent polymorphonuclear leukocytes. The urine contained less bile, and the stools were no longer clay-coloured, and the Van den Bergh test gave a biphasic reaction of 6.6 mg. per cent. A transfusion produced little clinical improvement. The temperature ranged between 103° and 99°, and the leukocyte count rose steadily, as is shown in chart 2.

The patient remained very apathetic, and took little or no food, obviously going down hill very rapidly. On the 23rd of October, a very soft, long, diastolic murmur was heard over the second right costochondral articulation and along the

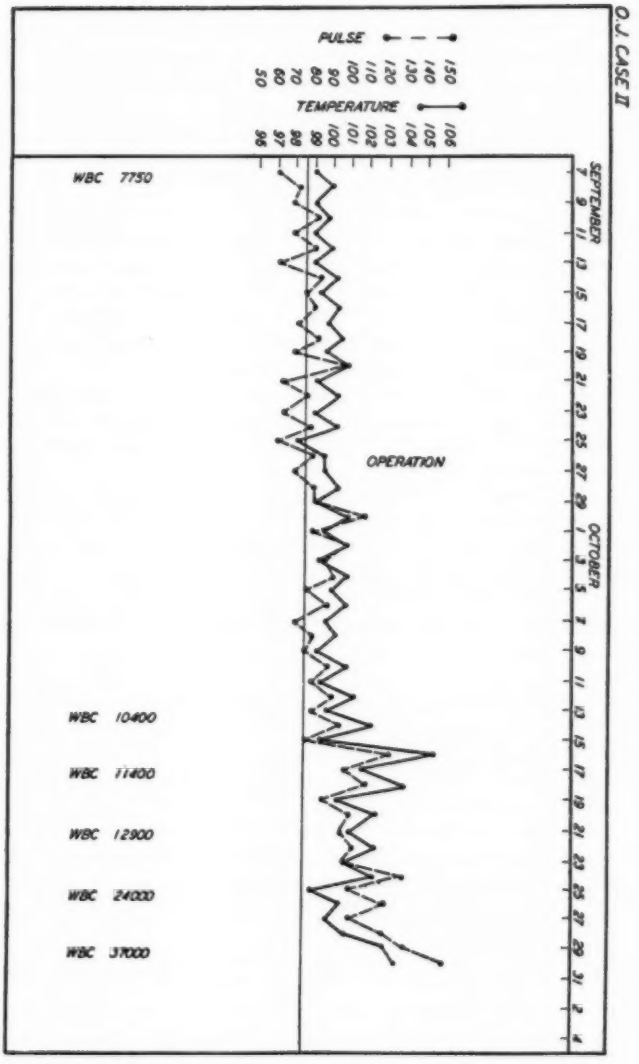

CHART 2. CASE 2, O. J., SHOWING DAILY VARIATIONS IN TEMPERATURE, PULSE RATE AND WHITE BLOOD COUNTS

left border of the sternum. On the 29th of October, there was a sudden hemiplegia and the left 4th finger became cold and blue. Scattered friction rubs appeared over both lungs without definite physical signs of consolidation; soon thereafter pulmonary oedema set in. The spleen was never palpable. Petechiae were not observed, and no red blood cells appeared in the urine. Blood cultures remained sterile. The leukocyte count rose to 37,000 on October 29th, and with acute cardiac failure, four weeks after operation, he died.

Autopsy 10634. October 29, 1929.

Anatomical diagnosis. Carcinoma of head of pancreas; metastases in liver; obstruction of pancreatic duct and extreme atrophy of remaining pancreas; obstruction of common bile-duct; jaundice; surgical cholecyst-gastrostomy. Acute aortic endocarditis (gonococcal); embolic occlusion of various arteries with infarcts of liver, spleen and kidneys; chronic arteriosclerotic nephritis. Thrombosis of pampiniform plexus; minor thrombi in femoral vessels; soft hemorrhagic infarctions of lung. Peculiar infarct of brain.

The body was that of a stoutly built negro man. On the left hand the 4th finger showed a bluish cyanotic nail. In the abdominal cavity the liver was found to project 8 to 10 cm. below the costal margin and to be dark green and studded with nodules.

Heart: Weight 360 gm. There were visible patches of sclerosis in the course of the coronary arteries. The endocardium and valves of the right side were normal. On the left side the mitral valve was slightly thicker than normal and there were one or two minute vegetations along the line of closure. The aortic valves were covered along the whole line of closure with thick rough crumbling fresh vegetations. There was no erosion of the valves but they were quite sclerotic, although there was no indication of syphilitic aortitis. There was no great insufficiency, but the valves were held apart and incapable of closing properly on account of the rough vegetations. The myocardium of the left ventricle measured 18 mm. and was rather soft. The wall of the aorta was delicate and normal in appearance except for a few flecks of fat deposit.

The left lung was in general air-containing. At the lower outer edge of the lower lobe there was a rather swollen area of a dark red color. On section it was soft and moist and the artery reaching it contained a thick dark thrombus. In the right lung there was a similar area. The spleen weighed 120 gm. and from the surface there projected irregular areas of a more opaque color which felt firmer than the remaining tissue and proved on section to be infarctions. The intestines were normal from the duodenum down.

The liver weighed 2200 gm. and everywhere over its surface projected roundish whitish nodules varying from 3 mm. to 2 cm. in diameter. On section the whole substance of the liver was studded with masses of tumor tissue. One of the main branches of the hepatic artery was obstructed by a dark red adherent thrombus producing a triangular area of the liver corresponding with the distribution of this vessel which was deep red and hemorrhagic and almost liquified in the center.

In the head of the pancreas there was a large mass, about 8 cm. in diameter, which was nodular, and the pancreatic duct was widely dilated. The pancreatic tissue distal to the tumor was almost completely atrophied. No metastases were found in the abdominal cavity except those in the liver.

The kidneys were equal in size, weighing together about 400 gm. The capsules stripped with slight difficulty leaving a roughened surface. There were some small sharply outlined punctate hemorrhages. On section several small pale infarctions were seen. The bladder, prostate, and seminal vesicles seemed normal and the testes were normal. There were several old thrombi in the femoral veins and thrombi in the various veins of the pampiniform plexus.

Microscopical notes. The liver contained many areas of adeno-carcinoma with much necrosis of the nodules. In the infarcted area practically everything was necrotic. The spleen showed an infarction with a zone of hemorrhage at the margin of the infarct. The tumor in the head of the pancreas had the appearance of an adeno-carcinoma similar to the nodules in the liver. The lungs showed in places edema and hemorrhage and sharply outlined areas of infarction. The kidneys showed no extensive occlusion of the glomeruli, although one or two had thrombosed capillaries, and arterioles were in some instances hyaline. On the aortic valve was a fresh hyaline vegetation but no bacteria could be seen in bacterial stains. Many areas in the brain were rarefied, leaving only a delicate network of neuroglia. Much of the gray matter was converted into a rarefied tissue with loss of ganglion cells and great concentration of thick-walled capillaries.

No growth of bacteria was obtained from the heart blood but in smears from the aortic valve gram-negative diplococci were seen and a gram-negative coccus which did not ferment dextrose was grown from the vegetations on the aortic valve.

Discussion

Throughout the early weeks of observation of this patient the diagnosis seemed perfectly clear. He obviously had long-standing arteriolosclerosis with hypertension and an obstructive jaundice shown at operation to be due to a tumor in the head of the pancreas. When first seen, the only abnormal findings about the heart were those indicating slight enlargement of the left ventricle and dilatation of the aorta. The fever which followed operation was an obscure feature. Finally, the occurrence of a definite aortic diastolic murmur which had never been present before, the continued fever with leukocytosis, general intoxication, progressive anaemia and peripheral arterial emboli suggested the diagnosis of acute aortic endocarditis. Again cultures from the blood both before and after death gave no growth. But the demonstration of gram-negative diplococci in smears from the aortic valve vegetations and the recovery of a gram-negative coc-

cus on culture, which would not grow on plain agar and which did not ferment dextrose, is strongly presumptive evidence that the endocarditis was due to a gonococcus.

It is further noteworthy that the patient gave a definite history of one attack of acute gonorrhea thirty-five years before his fatal illness but at post-mortem examination no focus could be found which might have served as a source for the terminal infection.

Case III. Abscess of the liver and septicaemia. M. K., *aet.* 36, colored laborer, Unit 27,614, was admitted to the hospital October 23, 1929, complaining of "fever" and died November 14, 1929.

History. The family history was not contributory and the patient had always enjoyed excellent health. There had been no symptoms referable to the gastro-intestinal system of any sort until the onset of the present illness. At the age of 17 he had had an acute gonorrheal urethritis which cleared up rapidly without complications. While in the army, however, in 1917 he received 6 intravenous injections for what he was told was "bad blood." He dated his present illness with accuracy to sixteen days before admission when he was awakened from a sound sleep by a shaking chill and a profuse sweat. The following day, however, he got out of bed but was content to sit around the house without doing very much because he "ached all over." The following morning he was worse. He had severe headache, dizziness, chilly sensations and diffuse abdominal pain which was not severe. His temperature was 105° but fell rapidly to normal on that day, the fall being accompanied by a profuse sweat and prostration. For the next 12 days the symptoms noted above continued, but none of them was very conspicuous. The patient felt "knocked out" and weak, and his temperature ranged from 99° in the morning to 101° or 102° in the evening. Three days before admission he was worse; the headache was more severe and the temperature was up and down two or three times a day and was accompanied by moderately severe chills. The day before admission nausea and vomiting, anorexia and constipation set in.

Physical examination. Temperature 102.5°, P. 120, R. 25, B. P. 110/65. He was intelligent, alert, well nourished, did not appear to have lost weight and was apparently in no distress. The skin was clear, the skeleton was normal, there was no tenderness over the paranasal sinuses or mastoid regions, there was no evidence of infection in the nose and throat and the ocular fundi showed no abnormalities. The peripheral lymph nodes were not enlarged, the heart sounds were all clear and easily heard and were not accompanied by murmurs.

The abdomen moved well but was moderately distended. There was slight diffuse abdominal tenderness and rebound tenderness with muscle spasm especially in the right upper quadrant. The liver dulness extended from the 5th rib to a point just below the costal margin in the mid-clavicular line where a hard firm

edge which was not tender could be felt. Several observers felt an indefinite mass in the epigastrium but it was not convincing. The neurological and rectal examinations revealed perfectly normal findings.

Blood: Hb. 75 per cent, R. B. C. 4,100,000, W. B. C. 18,000 with 84 per cent polymorphonuclear leukocytes. *Urine:* specific gravity 1.015, sugar, albumin negative; no casts, white blood cells or red blood cells were seen in the sediment.

Several hours after admission the temperature rose to 105.2°F. and the leukocyte count to 24,000, and after a consultation with the surgical staff it was deemed inadvisable to postpone an exploratory laparotomy.

Accordingly, he was taken to the operating room and under gas-oxygen anesthesia the abdomen was opened and a thorough exploration was made with absolutely normal findings except that the liver extended one or two fingers' breadth below the right costal margin, though it was perfectly smooth and was thought to be of normal consistency.

The patient recovered from the operation rapidly and several days later was transferred back to the medical service. The temperature and leukocyte counts are shown in chart 3. The high fever with striking intermissions, the leukocytosis and general prostration without specific complaints continued. Repeated careful physical examinations failed to reveal anything of note. Throughout his illness the possibility of a solitary liver abscess was frequently discussed, though no positive diagnosis was made. Repeated blood cultures during the early course of his disease gave no growth. Agglutination tests against organisms of the brucella melitensis group and enteric group were negative. X-rays of the chest revealed nothing abnormal. The Wassermann test was negative. Repeated cultures of the urine were sterile and those from the stools revealed no organisms of the typhoid or dysentery groups. A blood culture on November 8, 1929, and again on November 11, 1929, revealed a few colonies of gram-negative diplococci which would not grow on plain agar, were not agglutinated by anti-meningococcus serum but were agglutinated by immune gonococcus serum in a dilution of 1:320 and by the patient's own serum in a dilution of 1:640. The blood count fell rapidly and on the 6th of November, 1929, had fallen to R. B. C. 2,360,000, Hb. 55 per cent. The leukocyte count remained constantly around 25,000. The blood smears were repeatedly searched for the presence of malarial parasites but none was found and repeated examinations of the urine did not reveal any evidence of a urinary tract infection. Adequate doses of quinine had no effect upon the fever. Finally, from emaciation, prostration and general intoxication, he died on November 14, 1929.

Anatomical diagnosis. Abscess in right lobe of liver; infected thrombus in branch of hepatic vein; infected infarct of right lung. Acute splenic tumor. Peculiar mottling of left kidney with hyaline thrombosis of capillaries and partial thrombosis of renal veins.

The body was that of a well developed muscular negro without rigor mortis. The peritoneal surfaces were smooth and glistening and the liver extended 4 cm.

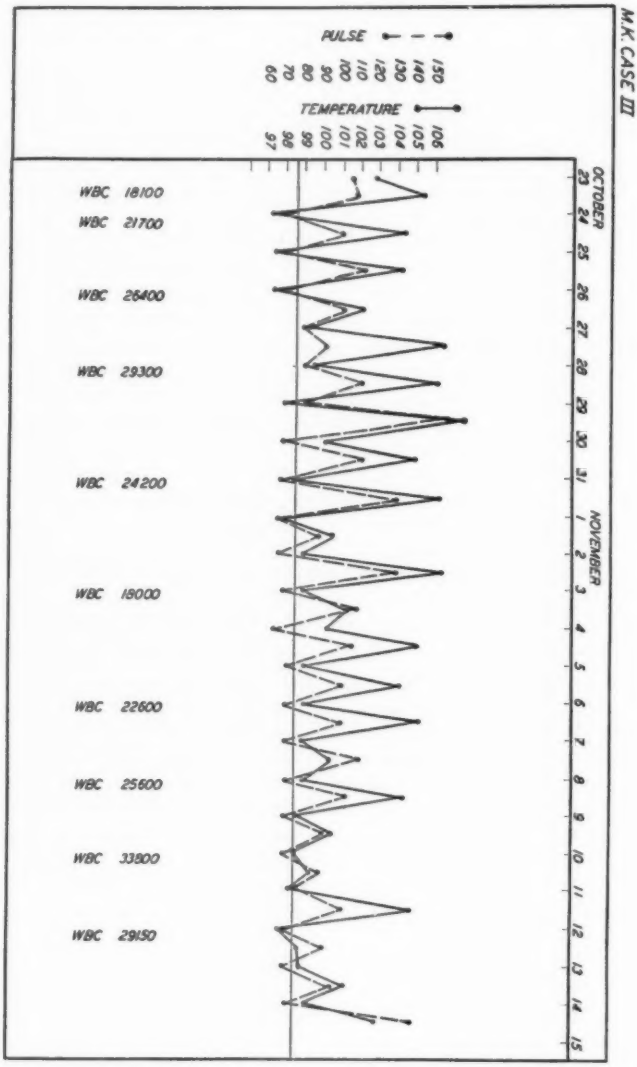

CHART 3. CASE 3, M. K., SHOWING DAILY VARIATIONS IN TEMPERATURE, PULSE RATE AND WHITE BLOOD COUNTS

below the costal margin. The pericardial and pleural cavities revealed nothing remarkable. The heart weighed 400 gm. and was moderately dilated, but the myocardium and endocardium seemed to be perfectly normal. The left lung was normal. In the lower posterior portion of the right lung there was a firm wedge-

FIG. 1. CASE 3. ABSCESS OF THE LIVER

shaped area covered by a thick layer of yellowish dry fibrin, and the pleura was dark red and flecked with hemorrhage. On section the part of the lung near the margin was dark red and firm, the proximal part was grayish red and in it were several smaller gray opaque areas four to six mm. in diameter resembling abscesses. No tuberculosis was found in the peribronchial lymph nodes.

The spleen weighed 310 gm. and was bluish red on the external surface. On section the margin retracted, the pulp was soft and grayish-red, the trabeculae were less prominent than usual and the Malpighian bodies were indistinct. The intestines, stomach, pancreas and adrenals were normal. The prostate showed no lesions. The right kidney weighed 160 gm. and the left 220 gm. The right kidney appeared perfectly normal. The left was soft and was more opaque in appearance than the right one. Over the surface there were numerous red mottlings and the cortex was thicker than on the right, the striae were blurred and the glomeruli were indistinct.

The liver weighed 2400 gm. and was quite soft in consistency. It was dark reddish-brown in color. On section the tissue was soft and the lobulations were pronounced; the center of each lobule was red and the periphery showed a dull gray tint. Exuding into the larger hepatic veins was yellowish purulent material which on closer examination was found to come from a large branch from the dorsal part of the right lobe of the liver near its entrance into the vena cava. A section made through a soft friable portion of the right lobe revealed a plugged hepatic vein leading into an abscess with which it communicated. The plugged portion of the vein contained a soft gray purulent thrombus. The abscess filled with thick yellowish pus, while partially collapsed, measured about 5 cm. in diameter. In the vicinity of this abscess were numerous yellow masses, some 1 to 2 cm. in diameter with small softened abscesses in their centers. A similar encapsulated mass with central softening was found between the thickened liver capsule and attached to the diaphragm (see figure 1). The brain was not examined.

Microscopical notes. The heart, pancreas, adrenals, ureters, seminal vesicles, tonsils, lymph nodes, muscles and bones showed no abnormalities. Section of the lung showed an infected infarct in a larger area of lobular pneumonia. The blood vessels leading into the area were infected and their walls were necrotic. They were filled with a purulent material probably representing a softened thrombus and within the vessels a few gram-negative cocci were clearly distinguished. In the area of pneumonia there were gram-positive as well as gram-negative cocci, some diplococci.

Sections from the spleen showed typically the appearance of an acute splenic tumor. Within the prostate, after a little search, areas could be found where the glands contained leukocytes within some of which gram-negative diplococci were seen.

Sections from the left kidney showed swelling and disintegration of the epithelial cells but no definite necrosis. There were thrombi in some of the small pelvic veins and what appeared to be thrombi composed of fibrin and a few leukocytes in numerous capillaries in the pyramids.

Liver: The contents of the abscess consisted of rather poorly preserved leukocytes, albuminous coagulum and large vacuolated phagocytic cells. There were numerous prolongations of the abscess cavity which appeared as a series of abscesses. The liver about the abscess was greatly scarred and beyond showed chronic

passive congestion probably the result of pressure. Several sections showed the infected large hepatic veins lined with granulation tissue and containing a purulent material. Few bacteria could be found but in the bacterial stains there were definite gram-negative cocci and diplococci. Cultures from the material, however, did not develop any organisms. Careful study of the sections from the region of the abscess revealed no amoebae.

Discussion

This case, one of great clinical interest, illustrates in a dramatic way the confusion and the difficulties that may and often do beset our interpretation of the subjective symptoms and the physical signs, or rather the lack of available physical signs.

The patient was admitted with symptoms highly suggestive of an acute intra-abdominal inflammatory process, with localized tenderness, muscle spasm, leukocytosis and high fever. We believe that the decision to explore the abdomen was not only the correct procedure, but that, under similar circumstances, no other decision would be justifiable. The fact that nothing abnormal was found at the operation beyond the somewhat enlarged liver extending only just below the costal margin, undoubtedly influenced our reasoning in connection with the subsequent developments.

Throughout the remainder of his illness the persistent fever of septic type, the leukocytosis and the progressive anaemia were the conspicuous features. The absence of all pain and of demonstrable abdominal tenderness, after recovery from the exploratory operation, was constantly commented upon.

Recalling occasional similar instances, when, in the absence of all convincing signs except a slightly enlarged liver, a fever of septic type, leukocytosis and progressive anaemia, a solitary liver abscess has subsequently been found, this possibility was discussed at length and insisted upon on more than one occasion. There was, however, little but negative evidence to support this view, and such a definite clinical diagnosis was not established. No exploratory liver punctures were attempted, though from the pathological evidence it would seem that the abscess might have been reached in this way.

On the eighteenth day after admission the blood cultures were reported positive for the first time, a small gram-negative diplococcus having been recovered following a special technique which included a

long incubation period. This organism had the morphological, biological and cultural characteristics of the gonococcus and it was considered as such. At this time the clinical interpretation that naturally suggested itself was that we were dealing with a gonococcus septicaemia arising from some concealed focus in the genito-urinary tract. This view was maintained by some in spite of the inability to demonstrate similar organisms from the urethra or from material obtained by massage of the prostate. The fact that the diplococcus recovered from the blood stream proved very difficult to grow, lent a certain plausibility to this opinion, though in many ways at the time the evidence in favor of a focus of infection in the genito-urinary tract seemed unsatisfactory to some who followed closely the clinical course of the disease. The patient's general condition grew steadily worse and he died on November 14th after an illness of thirty-seven days, dating from the onset of the first symptoms.

An autopsy was obtained and the pathological findings serve to explain the obscure clinical features. This case illustrates well the possibility of a liver abscess in the presence of such a clinical course as that outlined above, and also emphasizes the unimportance of a history without any previously known inflammatory abdominal lesion. That liver abscess may, and frequently does occur, without any suggestive evidence in the history of the source of the infection should be remembered. Its origin may be very obscure (6).

SUMMARY

It is significant that all of the three cases cited occurred in negroes, a fact consistent with the general racial incidence of the disease as emphasized by Thayer (8), and which may have masked the evidence of any skin lesions so frequently an accompaniment of gonococcal septicaemia. No suggestive rose spots and no petechiae were observed in any of the three. As adding to the difficulty of diagnosis in these cases Dieulafoy (2) has described an eruption which at the beginning may have every appearance of typhoid rose spots, though later shown to be polymorphic in character.

In this connection it is of interest that Thayer (9) in his communication of 1905 describes an instance of gonococcal septicaemia without endocarditis, with positive blood cultures, and recovery, in which "a

few rather suspicious papules on the abdomen suggestive of rose spots though not wholly typical" were noted. In a second instance of gonococcus septicaemia with ulcerative endocarditis and death, reported at this time, he describes further the occurrence of "small elevated red spots which disappear on pressure, and resemble somewhat rose spots except for their size which is 5 to 6 mm. in diameter, scattered over the abdomen, back and lower chest and to a lesser extent on the arms." In the white patients of Thayer's series (8) petechiae were noted in 54.5 per cent.

In the third case of our group the possibility of enteric fever or an infection with brucella abortus was seriously considered, a suspicion quickly put at rest by the repeatedly negative clinical tests. We have referred to the occurrence of skin eruptions in gonococcal septicaemia solely to emphasize their importance in adding to the uncertainty of diagnosis that may arise early in the course of these infections. As Thayer (*loc. cit.*) has so well put it, "a true gonorrhoeal septicaemia in cases in which there is no evidence of local complications may run a course not at all similar to that of typhoid fever." It should, perhaps, be emphasized that in none of the reported cases of gonococcal septicaemia has the leukocyte count been below 8000 per cu. mm. (8) which helps to exclude uncomplicated typhoid fever.

Our first case was an extraordinarily virulent infection with multiple joint involvement and a progressively fatal course. Apart from the question of diagnosis, the chief clinical interest lay in the interpretation of the endocardial signs; as to whether or not we were justified in making a diagnosis of acute endocarditis. In the presence of the grave anaemia and in the absence of any change in the character of the systolic murmur, as followed from day to day, such an interpretation was not considered justifiable, as was later confirmed by the autopsy findings.

The second case, complicated to be sure by the presence of a pancreatic tumor, illustrates the development of an acute gonococcal endocarditis and general septicaemia in an individual who gave no history of any Neisserian infection for 35 years, an astonishingly long latent period if we accept the facts as accurate. Neither during life nor at the necropsy was there found any evidence suggesting the origin of this acute virulent outbreak from a presumably quiescent

focus. Writing in 1922 (10) Thayer says "but little evidence could be obtained as to the relation of the onset of the symptoms to the stage of the initial local infection. In fifteen instances the relation to the time of onset of the specific urethritis was uncertain. In several instances all traces of the urethritis had disappeared." The longest established latent period that we have found in the literature was four years (9). That it is possible for the gonococcus to lie latent over a period of 35 years seems almost incredible. It would be extremely interesting if there were any way by which we could verify the accuracy of the history.

We wish to emphasize the significance of the cardiac sounds, and the importance of the appearance of the diastolic aortic murmur in this case, as the sole positive clinical evidence upon which the diagnosis of acute endocarditis could be made. Followed carefully from day to day, the heart sounds were everywhere loud and clear; the second sound at the aortic area was accentuated, but there was no diastolic murmur audible. A low-pitched systolic murmur heard over the precordium throughout was considered as unimportant. On October 23rd, forty-seven days after the patient first came under observation, a low pitched diastolic murmur of long duration, which subsequently increased in intensity, was first heard over the aortic area and along the left border of the sternum. Followed in six days by a series of emboli there could be no doubt as to the interpretation of the cardiac signs. The significance of the development of a diastolic murmur in such cases as evidence of an acute endocarditis is all important. It should not be forgotten, however, that endocarditis may be present in the absence of any murmur, and that in these grave septicaemias with extreme anaemia there may be entire absence of even any haemic murmurs. This point has been emphasized by Osler (3, 5). Such would be the exact antithesis of the problem presented by the first case cited.

Abscess of the liver due to the gonococcus is a rare occurrence. We have been able to find but two such cases in the literature, that reported by Roughton (7) occurring in a young woman following a pelvic infection and the instance reported by Bousfield (1) in a young soldier of the Egyptian Army. In the first of these the history of the pelvic abscess and the morphological characteristics of the organism

recovered, but not grown, is fairly convincing. In the second case there was no history obtainable of any previous gonococcal infection and early in the course of the illness the local lesion was considered as a tropical abscess. Surgical intervention and free drainage failed, however, to confirm this opinion. The organism recovered had all the characteristics of the gonococcus, though its identity was not established by culture. The patient made a good recovery.

We believe that there can be no question as to the nature of the infectious agent in the three cases we are reporting, all instances of a peculiarly virulent gonococcal septicaemia. They illustrate in a dramatic way three very different types of evolution of this disease, the possibility of an unusually long latent period, and the very exceptional occurrence of a primary liver abscess and the possibility of uncomplicated blood-stream invasion.

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A CASE OF BILATERAL PARALYSIS OF THE GLOSSOPHARYNGEAL AND VAGUS NERVES IN MAN[1]

ORTHELLO R. LANGWORTHY

From the Sub-department of Neurology, the Johns Hopkins University

This case is thought to be of considerable interest in that isolated, bilateral paralysis of the glossopharyngeal and vagus nerves in man, due to involvement of the lower motor neurones, is practically unknown; we have been unable to find a similar case in the literature. Very perplexing problems in diagnosis, in localization of the lesion and in picturing the pathological changes presented themselves and the nature of the morbid process is not yet entirely clear.

History. The patient, W. L., a colored man of 58, came to the hospital on December 13, 1930 and died on December 25, (J. H. H. Unit 34561). He was first seen in the laryngological clinic where he complained of hoarseness of six weeks' duration and difficulty in swallowing for three and a half weeks. The family history was non-contributory. He had always enjoyed robust health until the beginning of the present illness. Forty years before he had had a primary genital sore. He took medicine by mouth given by a friend but no other treatment. There had been no other manifestations of lues. He married in 1913 and his wife is living and well at 45. She has had no children and no miscarriages, although there had been one child by a previous marriage. The patient drank whiskey quite regularly until five years before his death.

He was perfectly well and able to work until three months before he came to the hospital. At that time he was troubled with a frontal headache which was very severe; this lasted continuously for about a week. He had had no fever, vomiting, ocular disturbances, stiffness of the neck, loss of consciousness or convulsions.

Seven weeks before he came to the hospital he developed a head cold with a post-nasal discharge. Then the hoarseness gradually appeared over a period of two weeks. For the last five weeks before admission, he had completely lost his voice and been unable to speak above a whisper. There had been no remissions in the symptoms. He articulated perfectly well.

Three and a half weeks before admission he began to have difficulty in swallowing solid food. He could chew the food but could not get it past his throat. He could, however, wash it down by drinking liquids. More recently, for the last

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two weeks, his diet had been entirely limited to liquids. Ten days before coming to the hospital, fluids began to regurgitate through the nose so that only about half would go down the throat.

There was constipation for the last four weeks before hospitalization although before that time his bowels had always been regular.

Since the onset of the illness there had never been any cough or any pain in the throat. There was no drooling of saliva from the mouth. The patient was rather dull mentally, but seemed to be fairly clear about the major facts in the history.

General physical examination. A careful examination revealed few important contributory findings aside from the abnormalities of the nervous system. Apart from the neurological examination, the abnormal physical findings were, in summary, as follows. The patient was undernourished and of low mentality. The skin was dry and scaly. There were opacities in both lenses and vision was diminished. The retinal arteries were narrowed and there was an arcus senilis. Marked dental caries was present. The heart was somewhat enlarged; there was a systolic murmur at the apex. There was an old penile scar.

Neurological examination gave the following information.

Cranial nerves. No. 2. Vision was somewhat diminished as a result of corneal opacities. The optic discs were of normal color and the edges were sharply defined. The arteries were definitely narrowed and tortuous; the veins were dilated.

Nos. 3, 4 and 6. The pupils were irregular, unequal; the right was larger than the left and both reacted sluggishly to light but well on accommodation. Extraocular movements were normal. There was no strabismus and no nystagmus.

No. 5. The corneal reflexes were active and equal. Both the motor and sensory portions of the trigeminal nerve were normal.

No. 7. The left nasolabial fold was not as marked as the right and there seemed to be some weakness of the facial muscles on the left side.

No. 8. The patient could not hear the watch held close to the ear but could hear the low conversational voice. There appeared to be some middle ear disease; bone conduction was better than air conduction.

Nos. 9, 10 and 11. There was a loss of sensation over the soft palate and the back of the pharynx; the gag reflex was lost. There was also a small area behind each ear but more marked on the right, where sensation was lost. The soft palate was paralyzed and no contraction of the musculature occurred. The nasopharnyx could not be shut off from the oral cavity. Fluids regurgitated through the nose. Articulation was normal but phonation was lost and the patient could not speak above a whisper. Only liquid food could be swallowed. The patient was constipated for the first time in his life. When he was examined in the outpatient department, the heart was irregular but on the ward the rhythm was normal.

There was some weakness of the sternocleidomastoid and trapezius muscles on the right, and winging of the right scapula.

No. 12. The tongue deviated to the right. It showed a coarse tremor but no atrophy or fibrillary twitchings.

The *motor system* showed few abnormalities. The muscles were fairly well developed and the strength was good. There were no abnormalities in tonus. No local atrophies or fibrillations of the muscles were observed. There was a tremor of the outstretched hands. The finger-nose test showed a very slight incoordination on the right, otherwise there was no ataxia. There was no Romberg. The gait was normal.

Reflexes. The deep reflexes in the arms were active and equal. The upper abdominals were active; no responses were obtained from the lower quadrants of the abdomen. The knee and ankle jerks were active and equal. The plantars were flexor. There was no clonus.

Sensation. It was difficult to test sensation in this patient. Aside from the abnormalities reported in connection with the cranial nerves, the response to pin-prick, cotton wool, vibratory and sense of passive movement was everywhere normal.

In *summary*, the neurological examination revealed abnormalities of the cranial nerves. There was bilateral paralysis of the glossopharyngeal and vagus nerves. The function of the left facial nerve was impaired and there was weakness of the spinal accessory and of the hypoglossal on the right side.

Laryngeal examination in the outpatient department, revealed the following findings. The larynx rose fairly well on swallowing. The epiglottis was not congested but lay over the vocal cords in such a way that it was difficult to see them on expiration. The epiglottis flopped to and fro, making a low-pitched sound. There was complete paralysis of the left and partial paralysis of the right vocal cord. There was little response to stimulation of the palate and posterior pharyngeal wall. A second examination on the ward showed a complete paralysis of the left vocal cord and almost complete paralysis of the right.

The *laboratory findings* were as follows: The red blood count was 3,830,000 hemoglobin 78 per cent. The while blood count on admission was 4250 with a normal differential count.

The blood Wassermann was positive. The spinal fluid pressure was 10 mm. The Queckenstedt test was normal. The fluid was clear and colorless. There were 2 cells, and the Pandy was negative. The spinal Wassermann was negative as was also the colloidal mastic test. Culture of the spinal fluid gave no growth. Non-protein nitrogen in the blood was 36 mgm. per cent.

The administration of two milligrams of atropine produced only an increase of 8 to 10 beats in the pulse rate.

The electrocardiogram showed a normal sinus rhythm. There was an occasional ventricular extrasystole.

Course in hospital. Soon after the patient entered the hospital he developed an aspiration bronchopneumonia. A heavy growth of staphylococcus albus was grown from the sputum. X-ray plates showed definite signs of pneumonia in

the right lung. The temperature and white count rose. He died on December 25, 1930.

The *clinical diagnosis* was arteriosclerosis, hypertension, syphilis (latent), bilateral paralysis of the ninth and tenth cranial nerves and bronchopneumonia.

There was always considerable doubt as to the etiology of the bilateral glossopharyngeal and vagus nerve paralysis. The vagus and glossopharyngeal nuclei cover a considerable longitudinal area in the brain-stem and it is difficult to imagine a lesion in the medulla that would not produce many attendant symptoms that were absent in this case. If the glossopharyngeal and vagus nerves or roots were involved, this must have occurred close to the nervous system, for the branches to the palate are given off relatively early. A localized syphilitic meningitis was first considered but was ruled out by the negative spinal fluid. It might be possible to imagine a syphilitic process just outside the dura at the point where the nerves enter the jugular foramina but it would be unusual to have a bilateral involvement of this kind. Abnormalities in the mediastinum would not explain the paralysis of the palate. Not only was it puzzling to localize the lesion but it was impossible to be sure whether the underlying etiological factor was syphilis or arteriosclerosis.

The *post-mortem examination* revealed the following findings (No. 11,773). The body was that of a 55-year-old-negro. It weighed 47.5 kilos. The man was well developed but poorly nourished. The epitrochlear and inguinal lymph glands were slightly enlarged, hard and discrete.

The heart weighed 400 grams and was of about normal size. The heart muscle showed a few scattered, grayish-yellow flecks here and there. The coronary vessels were all patent. Their walls were greatly thickened and the intima roughened. They were all markedly tortuous and dilated.

The pleural surface of both lungs was reddened over the lower half and there was a small amount of sticky white exudate on the surface. Moreover, there were minute white areas of pin-head size scattered over the lower surface of the pleura. The bronchi were all somewhat dilated and contained yellowish, frothy material. The bronchial glands were markedly enlarged. The lower lobes of the left lung and the lower and middle lobes of the right lung contained patches of yellowish consolidation and the remainder of the lung was reddened but soft and appeared to be, for the most part, air-containing.

The capsule of the spleen was smooth and of a dull gray color. The cut surface was granular and grayish red. It was flecked with numbers of grayish-white dots.

The liver weighed 1300 grams. The capsule was smooth and glistening but again grayish-white dots could be distinguished on the surface of the liver, beneath the capsule. On section, the liver was pinkish-gray. The lobulations were distinct and the vessels normal in appearance.

The adrenals weighed 20 grams together and were slightly smaller than normal. On section, the medulla and cortex appeared normal.

The kidneys were surrounded by a small amount of fat. Each weighed 470 grams. The capsules were glistening, thin and stripped easily. The surface of

the kidneys was smooth and of a uniform, grayish-red color. The cortex was about 0.5 mm. thick. The striations were distinct and fairly regular. There were a few areas of distortion of the striations.

The mucosa of the stomach, duodenum, jejunum, ileum, caecum and colon was of normal thickness and appearance. The mesentery contained very little fat. The lymph nodes were uniformly and moderately enlarged, firm and discrete.

The pharynx, larynx and vocal cords appeared normal. The mucosa of the trachea was somewhat hyperaemic, more so in its lower third. The thyroid was of normal size and section through each lateral lobe revealed no abnormality. The vagus nerves could be followed through the neck and thorax and appeared normal.

The aorta contained many atheromatons deposits and the intima was roughened throughout. There were a few linear striations on the ascending portion. The large branches of the aorta were all tortuous, thick-walled, hard and dilated. The lumina were all patent.

The meninges covering the brain were slightly thickened over the vessels. The venous sinuses were opened and found to be patent. The vessels at the base of the brain were all markedly dilated, tortuous, hard and thick-walled. The basilar artery formed a deep groove in the pons. The hypophysis was of normal size and appearance. The meninges of the spinal cord appeared normal. Sections of the cord revealed no abnormalities.

When the brain was removed, there was an area on the right ventral surface of the pons which appeared distinctly softer than normal and it was believed that there was an infarct in this region. After the brain was hardened, no abnormality could be seen in the intact specimen and macroscopic sections through the pons showed no evidence of an infarct.

Microscopic examination revealed the following abnormalities. The heart muscle showed a few small areas of scarring. The individual muscle fibers were slightly hypertrophied. The endocardium and blood vessels appeared normal.

There were scattered areas of lobular pneumonia in the lungs; the alveoli in these places were filled with polymorphonuclear leucocytes and mononuclear cells and also with fat droplets. The phagocytic cells also contained much fat. Many of the bronchioles were filled with similar collections of cells. A collection of pink-staining, homogeneous substance filled many of the alveoli. The pleura was thickened in some places but showed no evidence of an acute inflammation. Giant cells containing fat were scattered here and there in the lung. One small tubercle was found, apparently old, for it was well encapsulated.

In the liver the cell columns around the central veins were farther apart than those around the portal veins, and the cells were smaller with more deeply staining nuclei. There were few encapsulated areas made up of epithelioid cells and lymphocytes which suggested tubercles. Around some of the portal spaces was a collection of lymphocytes.

The kidney showed a few scars beneath the capsule with dilated tubules between and obliterated tubules in the scarred areas. There were several glomeruli which

had become hyalinized and others were partially hyalinized. The blood vessels showed little abnormality.

In the spleen there were numerous tubercle-like lesions, often in the malpighian bodies, often in their margins. These lesions were fairly well encapsulated, small and composed of epithelioid cells, lymphocytes and giant cells in a connective-tissue framework. A few of the lesions apparently had friable, homogeneous centers. The capsule of the spleen was normal.

The pancreas was normal. There was one encapsulated tubercle-like lesion found in the adrenal. The mesenteric lymph nodes were large and were riddled with tubercle-like lesions. Sections of the stomach, duodenum and intestine revealed no abnormalities.

There was considerable connective tissue in the anterior lobe of the hypophysis and there were a few small areas suggesting tubercles. At the edge of the posterior lobe was a definite tubercle containing epithelioid and giant cells.

Sections of all the organs were stained for spirochaetes and tubercle bacilli but neither were found.

Examination of the nervous system was first focused on the tortuous arteries at the base of the brain, for the question arose as to whether the nerves could be compressed in any way at the point where they left the brain-stem. The arteries are shown in figure 1. It is seen that the vertebrals are very tortuous and sclerotic and lie rather far laterally so that the hypoglossal nerves curve around their lateral surfaces. The lumina of the vessels are large, and numerous plaques are present in the walls. The basilar artery is seen to be embedded in a groove formed in the ventral surface of the pons. The cerebellar branches show the same arteriosclerotic changes, but no arteries press upon the roots of the glossopharyngeal or vagus nerves. It was felt, therefore, that the tortuosity of the blood vessels on the ventral surface of the brain-stem would not account for the paralysis. A photomicrograph (fig. 2) shows a small portion of the wall of the basilar artery. There is a marked thickening of the intima.

Many sections of the central nervous system were cut and stained in different ways. No abnormalities were demonstrated in the fore-brain. Sections of the medulla showed the most obvious changes; these extended into the pons and throughout the length of the spinal cord. There was infiltration of lymphocytes around the walls of some of the small blood vessels; this infiltration was most marked in the medulla (fig. 7). It reached its greatest development in the vessels just beneath the surface of the fourth ventricle but was also scattered through the whole brain-stem. There were other groups of round cells (lymphocytes and phagocytes) which appeared to be unassociated with the blood vessels. A low-power photograph of one such area, found among the nerve cells of the inferior olive, is shown in figure 5 and a high-power photograph of another in figure 6.

Both the autonomic and the somatic motor cells of the glossopharyngeal and vagus nerves showed very definite signs of chromatolysis. Cells from the ambiguus nucleus of the vagus nerve are shown in figure 4. It will be noticed that the cell nucleus lies at the edge of the cytoplasm and that there is a marked loss of

chromophilic granules. Similar changes were observed in many cells of the facial, accessory and hypoglossal nuclei. Such changes may, of course, be due either to injury of the nerve cell or to injury to the nerve fibers outside of the nervous system.

Sections were stained by the Spielmeyer technique to demonstrate medullated fibers. The fibers appeared quite normal except in the dorso-medial portion of the brain stem below the lower portion of the fourth ventricle. In this region there was a complete loss of medullated fibers in the region of the dorsal nucleus of the vagus and medial to this area. This is demonstrated in figure 3. The dorso-lateral portion of the medulla is on the left and here the medullated fibers are quite normal and stain a deep black. Mesially the myelin sheaths are completely lost. In this area very numerous myelin bodies are seen in hemotoxylin-stained sections.

There was a considerable infiltration with lymphocytes around the glossopharyngeal and vagus rootlets after they emerge from the medulla and some infiltration of the pia-arachnoid around the whole brain-stem.

No spirochaetes could be demonstrated in sections of the brain-stem.

DISCUSSION

Many questions arise in connection with the anatomical study of this case. Is the morbid process in the central nervous system identical with that demonstrated in the spleen and are both tuberculous in origin? No tubercle bacilli or spirochaetes could be demonstrated in any of the sections, although a careful and prolonged search was made. The cause of the disease outside of the nervous system is still in doubt. It is certain, however, that the lesions in the central nervous system do not suggest tuberculosis in any way. There were many tubercle-like bodies in the pleura and spleen and almost none in the lungs or liver. This is extremely unusual in a case of disseminated tuberculosis. Probably the most that can be said is that there was an encephalitis in the region of the brain-stem.

Since the patient was known to have syphilis it is very tempting to consider this the cause of the brain lesions. The spinal fluid, however, was normal. The abnormal reactions of the pupils certainly show that at some time during life there had been syphilitic lesions in the nervous system. It seems justifiable to question the cell count, for there was considerable infiltration of lymphocytes around the rootlets of the glossopharyngeal and vagus nerves. The abnormalities in the medulla were similar in all respects to those found in the cerebral

cortex in cases of paresis. No spirochetes could be demonstrated in the present case.

The process in the medulla was a diffuse one and it is difficult to understand why the nuclei of the cranial nerves were injured while the long pathways traversing this region and the cells giving rise to similar correlation tracts were quite undamaged. Such specificity in the group of fibers injured is characteristic of syphilis. No one has yet explained satisfactorily why the posterior columns of the cord and the optic nerve are marked out for destruction in tabes. No inflammatory lesions, found at autopsy, throw light upon this question.

Paralysis of one or more cranial nerves is not unusual in cases of lues. It is commonly believed that the nerves are compressed in a basilar meningitis which is extremely localized or by a gummatous process in the meninges. Such an explanation seems extremely improbable. A tuberculous meningitis with the greatest thickening and matting together of the meninges at the base of the brain does not produce cranial nerve paralysis.

Indeed it may well be assumed that lesions of other cranial nerves in syphilis is often quite similar to that found with involvement of the optic nerve in tabes. Here, few changes are found in sections; there is often slight infiltration around the nerve similar to that occurring in the present case.

Syphilis seldom involves the glossopharyngeal and vagus nerves and more commonly induces paralysis of the nerves to the extraocular muscles of the eye or of the facial and trigeminal.

In the present instance the lesion is a diffuse one and no explanation is found for the localization of the injury to the nuclei of certain nerves.

Bilateral section of the vagus nerves in the neck is possible in animals; this lesion does not involve the upper branches of the nerve. No case of a similar lesion has been reported in man. It is interesting that there was no disturbances of cardiac rate or rhythm. Constipation was a feature of the disease, probably due to atony of the intestinal tract. The patient was on a liquid diet, which might possibly have aggravated the difficulties with defecation.

This case is presented because of its clinical interest due to the

bilateral involvement of the glossopharyngeal and vagus nerves. It seems quite clear that some toxic or infectious process has injured the neurones in the medulla without damaging the long pathways which travel through this region. Syphilis may be the etiological agent but this unfortunately has not been proved.

PLATE I

FIG. 1. SCLEROTIC AND TORTUOUS BLOOD VESSELS AT THE BASE OF THE BRAIN

FIG. 2. SECTION OF THE WALL OF THE BASILAR ARTERY SHOWING THE THICKENING OF THE INTIMA

FIG. 3. PHOTOMICROGRAPH OF A SECTION FROM THE LOWER PORTION OF THE MEDULLA STAINED BY SPIELMEYER'S METHOD FOR STAINING MEDULLATED NERVE FIBERS

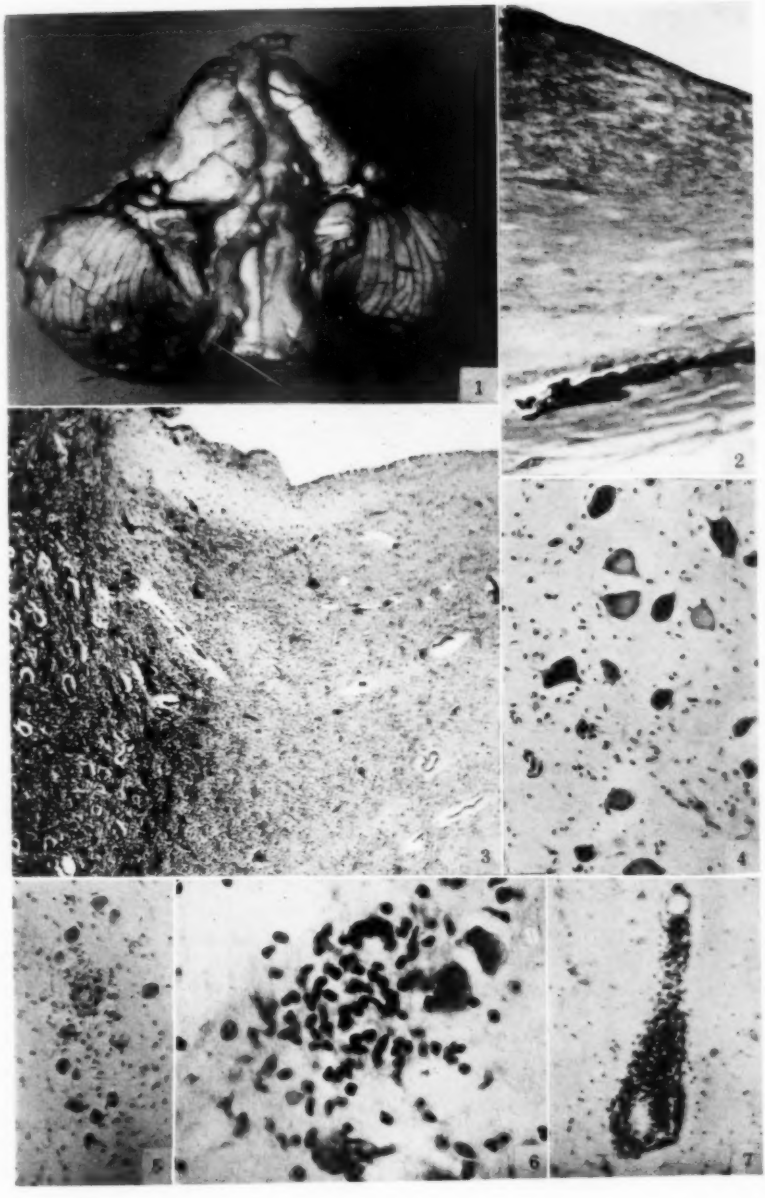
In an area just ventral to the lower portion of the fourth ventricle there was an area, including the dorsal nucleus of the vagus which showed a complete loss of medullated nerve fibers.

FIG. 4. CELLS OF THE NUCLEUS AMBIGUUS OF THE VAGUS NERVE SHOWING CHROMATOLYSIS

FIG. 5. COLLECTION OF LYMPHOCYTES AND ROUND CELLS IN THE MEDULLA

FIG. 6. HIGH-POWER VIEW OF A SIMILAR AREA OF INFILTRATION

FIG. 7. INFILTRATION WITH LYMPHOCYTES AND PHAGOCYTIC CELLS AROUND A SMALL BLOOD VESSEL IN THE MEDULLA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ANTERIOR PITUITARY INSUFFICIENCY (SIMMONDS' DISEASE)[1]

ROYALL M. CALDER

From the Department of Medicine, Duke University School of Medicine, Durham, North Carolina

HISTORICAL

In 1884 Fritsche and Klebs (1) recorded enlargement of the pituitary body in a case of gigantism, and Minkowski (2), in 1884, suggested that the pituitary might be related to acromegaly. The first series of cases showing that enlargement of the hypophysis was of etiological significance in cases of pathological overgrowth was presented in 1894 by Tamburini (3). Subsequent clinical and postmortem observations soon proved that over-functioning of the pituitary leads to gigantism and acromegaly, but the possible effects of insufficiency of this important structure remained obscure until experimental work by Paulesco (4) in 1907 demonstrated that removal of the pituitary in dogs was followed by a train of symptoms characterized mainly by weakness, loss of weight, and death—a condition to which the name "cachexia hypophyseopriva" was given.

In 1914 Simmonds (5) described the first clinical case exhibiting the syndrome observed in Paulesco's experimental animals. The patient was a 46-year-old woman, who at the age of 38 had been the victim of puerperal sepsis. Following this illness there was cessation of menstruation accompanied by muscular weakness, attacks of unconsciousness, and the general appearance of "premature senility." Necropsy showed atrophy of the kidneys, ovaries, pancreas, and liver ("Splanchnomikrie"), with necrosis and scar-tissue replacement of the anterior lobe of the hypophysis. Simmonds insisted that the destruction of the anterior lobe was the primary etiological factor in this case, and in 1916 (6) reported two other cases which, while not so typical as the first, nevertheless served to emphasize the importance of pituitary

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insufficiency as a cause of emaciation: The first of these two patients was a 58-year-old shoemaker who had suffered for two years from progressive cachexia without demonstrable cause, who finally died of pneumonia, and who at necropsy was found to have two tumors of the basophilic elements of the hypophysis, which had entirely replaced the substance of the gland; the second was a 9-year-old girl who died of conditions clinically simulating the emaciation of chronic tuberculosis, and who at necropsy was found to have a basophilic tumor of the pituitary that had completely destroyed the remainder of the gland substance. Even before Simmonds' descriptions, however, similar clinical pictures had been observed, and Graubner (7), in reviewing the clinical literature prior to 1925, was able to find six cases which antedated those of Simmonds. In all of these, various destructive processes were found in the hypophysis, although previous to Simmonds' reports it had not been recognized that the hypophysis was primarily at fault.

Meanwhile, attempts had been made, notably by Cushing (8) and by Crowe, Cushing, and Homans (9) to confirm Paulesco's work, but their results were inconclusive, perhaps because, as admitted by these authors, the removal was subtotal. It is significant, however, that in these latter experiments there occurred "remarkably rapid involution or actual degeneration of the thyroid and gonads." Adiposity was also observed as one of the sequelae, but subsequent work has shown that this symptom undoubtedly was the result of trauma to adjacent structures. Although Erdheim (10) had suggested that injury to the tuber cinereum might cause adiposity, the first experimental support for such an idea was furnished by Camus and Roussy (11) and by Bailey and Bremer (12), who in 1920–21 found that polyuria, adiposity, and disturbances of temperature regulation, as well as sexual dystrophy, could be produced by focal lesions of the tuber cinereum, without coincident injury to the pituitary body.

Inasmuch as the two distinct syndromes, "cachexia hypophyseopriva" and "dystrophia adiposo-genitalis," are seen clinically as the results of pituitary disease, it is important to determine whether they are both induced by disturbance of the pituitary body *per se*, or are caused by pathological changes in separate anatomical units. Suggestive as the above experimental observations were, it remained for P. E.

Smith (13), by the use of a very ingenious operative procedure, to adduce decisive proof for the assumption that the two conditions are dependent on totally different processes. He found that lesions of the hypothalamic region (tuber cinereum) of rats gave rise to a syndrome characterized by extreme obesity and atrophy of the genital system without any demonstrable change in the thyroid or suprarenal cortex. Ablation of the anterior lobe of the hypophysis, on the other hand, gave rise to an invariable syndrome, the main features of which were an almost complete inhibition of growth in the young animal and a progressive loss of weight (cachexia) in the adult; atrophy of the genital system with loss of libido sexualis; immediate cessation of the sex cycles in the female; atrophy of the thyroid, parathyroids, and suprarenal cortex; and a general physical impairment characterized by a lowered resistance to operative procedures, loss of appetite, weakness, and a flabbiness that readily distinguished the hypophysectomized from the normal animal. A number operated on at the time of sexual maturity died about five months later with the physical chacteristics of senility.

Smith's researches, therefore, furnish a well founded experimental basis for the clinical syndrome described by Simmonds.

The following cases, many of which are reviewed more extensively in in Graubner's article (7), have appeared in the literature:

Case 1, Ponfick, 1899 (14): Male, 47, shoemaker. Onset of illness at 32, with inabilty to work, pallor, symptoms somewhat those of myxedema, loss of pubic hair, psychic disturbances preceding death. *Necropsy:* Suprarenals, liver, and kidneys small. Anterior lobe of hypophysis replaced by degenerated glandular remnants in much scar tissue; posterior lobe not affected.

Case 2, Claude and Gougerot, 1908 (15): Male, 50. Loss of energy, falling of hair and teeth, atrophy of testicles, complete impotence, weakness, feelings of coldness, thickening and drying of skin, apathy, change of voice, pigmentation of skin and mucous membranes, low blood pressure. Death apparently from pulmonary tuberculosis. *Necropsy:* Cavernous tuberculosis of lungs. Testicles small, marked atrophy of prostate and seminal vesicles. Suprarenals small. Spleen small, containing tubercles. Microscopically the thyroid showed marked sclerosis, many caseous tubercles, only islands of alveoli. Hypophysis almost completely replaced by scar tissue.

Case 3, Sainton and Rathery, 1908 (16): Female, 32. Luetic. Typically myxedematous, no axillary or pubic hair. Skin thickened. Slow speech. Headaches, vomiting, apathy. *Necropsy:* Thyroid sclerotic. Suprarenals showed

much connective tissue in which scarcely a trace of glandular tissue was to be found. Genitalia atrophied. Hypophysis replaced by a cyst.

Case 4, Gougerot and Gy, 1911 (17): Male, 52, laborer, Following long-continued febrile illness, onset of muscular weakness, marked loss of weight, polydipsia, loss of libido, feeling of cold, brown discoloration of skin, falling of axillary and pubic hair. Atrophy of genitalia. Skin sclerodermic. Thyroid not palpable. *Necropsy:* Thyroid small, atrophic. No interstitial or reproductive cells in testicles. Capsule of suprarenals thickened and fibrotic. Hypophysis capsule thickened, much connective tissue in gland itself.

Case 5, Austregésilo, Pinheiro, Marques, 1913 (18): Male, 45. At 30, falling of hair. Difficulty in vision and hearing. Aged appearance, tall, emaciated. Pigmentation of skin of neck. Testicles atrophied. Blood pressure 50. Visual and auditory hallucinations. *Necropsy:* Small tuberculous foci in lungs. Spleen and liver small. Thyroid sclerotic with vacuolated colloid. Capsule of suprarenals thickened, zona glomerulosa atrophic. No cellular elements in testicles. Hypophysis showed considerable connective tissue, cells normal, vessels thickened.

Case 6, Falta, 1913 (19): Male, 55. High grade emaciation and cachexia. Skin pale and dry. Thyroid enlarged. No body hair. Atrophy of genitalia. Enlargement of sella turcica. *Necropsy:* Marked senile atrophy of upper and lower jaws with almost complete absence of teeth. Struma of thyroid with pressure atrophy of parenchyma. Atrophy of suprarenal cortex but not of medulla. Atrophy of testicles. Cyst of hypophysis with pressure atrophy of glandular structures and enlargement of sella turcica.

Case 7, Simmonds, 1914 (5): Female, 46, puerperal sepsis at 38, cessation of menstruation, muscular weakness, attacks of unconsciousness, anemia—"premature senility" Gradual down-hill course until at age of 46 there was coma and death. *Necropsy:* Atrophy of kidneys, ovaries, pancreas, and liver, and necrosis with scar-tissue replacement of hypophysis, particularly of anterior lobe.

Case 8, Maresch, 1914 (20): Female, 33. Apathy, weakness, emaciation. Falling of axillary and pubic hair. Temperature from 35 to 36 degrees Centigrade. *Necropsy:* Thyroid small, with much connective tissue. Anterior lobe of hypophysis replaced by connective tissue poor in cells.

Case 9, Schlagenhaufer (21): Female, 27. Great weakness, premature menopause. Slight tuberculosis of lungs. *Necropsy:* Slight pulmonary tuberculosis. Anterior lobe of hypophysis replaced by tuberculous granulation tissue.

Case 10, Simmonds, 1916 (6): Male, 58, shoemaker. Progressive cachexia for two years. Clinically, no abnormalities except mild secondary anemia. Terminal pneumonia. *Necropsy:* Two tumors of hypophysis, basophilic cells, which had entirely replaced glandular substance.

Case 11, Simmonds, 1916 (6): Female, 9. Symptoms suggesting chronic tuberculosis. Polyuria. *Necropsy:* Basophilic tumor completely destroying hypophysis.

Case 12, Fraenkel, 1916 (22): Female, 45. Moribund, marked emaciation and

cachexia, cessation of menstruation, death. *Necropsy:* Glandular portion of hypophysis atrophied and replaced by a connective-tissue mass.

Case 13, Elsberg and Krug, 1917 (23): Female. Case of cachexia hypophyseopriva plus hemianopsia, low temperature and blood pressure, cessation of menstruation. Not affected by feeding Armour's anterior lobe extract, but greatly improved by injections of pituitrin, first daily, then weekly, and finally monthly. Temperature and blood pressure were raised, visual fields practically cleared, and menses reappeared.

Case 14, Simmonds, 1918 (24): Female, 48, brought into hospital *in extremis*. Onset 18 years previously, following confinement: paralysis, cessation of menstruation, increasing weakness, loss of weight, gradual down-hill course, coma, death. *Necropsy:* Abdominal organs all small. Pituitary body only one-third normal size, due to atrophy of anterior lobe. Posterior lobe not altered.

Case 15, Simmonds, 1918 (24): Female, 35. Loss of axillary and pubic hair, senile appearance, wrinkled skin, cachexia. Terminal pneumonia. *Necropsy:* Abdominal organs small. Thyroid showed small islands of lymphoid tissue. Posterior and intermediate lobes of hypophysis not altered; anterior lobe converted into a mass of connective tissue.

Case 16, Fahr, 1918 (25): Female, 50. Pneumonia at 24, followed by menopause. Vomiting, cramps. *Necropsy:* Brown skin. Suprarenal capsule thickened, atrophy of cortex and medulla. Anterior lobe of hypophysis replaced by connective tissue, also calcification.

Case 17, Schaeffer, 1919 (26): Female, 22. Premature menopause. Cachexia. Vomiting. Lues. *Necropsy:* Skin rough. Axillary and pubic hair sparse. Spleen enlarged. Liver small. Suprarenals, uterus, and ovaries small. Hypophysis strikingly enlarged, microscopically showing necrotic foci with giant cells; no tubercle bacilli demonstrable.

Case 18, Reye, 1920 (27): Female, 50. Apathy, vomiting, falling of teeth, eyebrows, axillary and pubic hair, atrophy of genitals and thyroid, subnormal temperature, eosinophilia, positive blood Wassermann reaction. Antisyphilitic treatment effected considerable improvement.

Case 19, Hirsch and Jaffe, 1920 (28): Male, 55. History of gonorrhea and syphilis. At 40, pneumonia followed by great gain in weight. At 44, falling of beard and axillary and pubic hair. Disturbance of sexual functions. At 53, high grade weakness, insomnia, vomiting, falling of teeth. Dry, cold skin. Blood pressure 80/50. Emaciation. Terminal bronchopneumonia. *Necropsy:* Carcinoma of oesophagus, with metastases in lungs. Atrophy of thyroid and hypophysis, questionably due to a syphilitic inflammation.

Case 20, Hochstetter, 1922 (29): Male, 38, farmer. First symptoms were intense thirst, sleeplessness, headache, and impotence. Four years later, pains suggesting polyneuritis, extreme weakness, apathy, emaciation, low blood pressure, polydipsia, and polyuria. *Necropsy:* Induration of kidneys, liver, and lungs. Hypophysis, thyroid, testicles, suprarenals, and parathyroids were sclerotic and atrophied.

Case 21, Keilman, 1922 (30): Female, 20. Menopause at 16 following delivery. At 17, headache, vomiting, marked emaciation; meningitis (? pneumococcus). At 20, optic atrophy, polydipsia, somnolence. Strikingly pale, emaciated; no axillary or pubic hair. Secondary anemia. Wassermann reaction in blood negative. *Necropsy:* Cyst of hypophysis.

Case 22, Knoll, 1922 (31): Young male. Premature senility, falling of hair, decline of genital function. *Necropsy:* Embolism in anterior lobe of hypophysis.

Case 23, Lindemann, 1922 (32): Female, 34. Luetic. At 23, menopause. Falling of axillary and pubic hair. Fair state of nutrition. *Necropsy:* Atrophy of thyroid, pancreas, suprarenals, and particularly of genitalia. Hyperaemia and simple atrophy without marked sclerosis of anterior lobe of hypophysis.

Case 24, von Monakow, 1922 (33): Male, 60. Falling of all hair. Low basal metabolic rate. Oliguria. *Necropsy:* Anterior lobe of hypophysis almost completely destroyed by acute inflammatory process. High grade atrophy of testicles.

Case 25, Pribam, 1922 (34): Female, 32. Manual removal of placenta with puerperal sepsis. Loss of pubic hair, premature senility. Somnolence, subnormal temperature. *Necropsy:* Senile atrophy of abdominal organs. Anterior lobe of hypophysis showed hyalinized, sclerotic tissue; posterior lobe unchanged. Thyroid parenchyma almost completely replaced by scar tissue as result of chronic inflammatory process. Sclerosis of suprarenal cortex.

Case 26, Reinhardt, 1922 (35): Sex not stated. Fracture of base of skull with injury to hypophysis and resultant scar-tissue formation. Cachexia and rather sudden death after three and a half months.

Case 27, Lichtwitz, 1922 (36): Male, 19. Marked thirst and polyuria. Loss of interest. Headache, diminution of vision, decrease in size of genitalia, falling of axillary and pubic hair, cessation of growth of beard, change in disposition, bitemporal hemianopsia. Temperature 35.4 to 36.7 degrees Centigrade. Blood pressure 100. Polyuria was controlled with "Pituglandol."

Case 28, Lichtwitz, 1922 (36): Female, 31, luetic. Headaches, vomiting, polyuria, polydipsia, cessation of menstruation, falling of hair, loss of libido. Polyuria controlled with "Pituglandol."

Case 29, Lichtwitz, 1922 (36): Female, 41. Luetic. Following birth of second child, fever of two weeks' duration, then falling of pubic and axillary hair, anorexia, languor, amenorrhea, loss of libido. Thyroid small and hard.

Case 30, Jakob, 1923 (37): Female, 45. Symptoms developing gradually following last delivery at 35. Apathy; falling of axillary and pubic hair; pallor of skin with dryness and cold feelings; subnormal temperature; pulse 50. Weight 50 kilograms. Terminal delirium. *Necropsy:* Tuberculous meningitis. Thyroid showed much connective tissue. Suprarenals atrophied. Anterior lobe of hypophysis showed fibrotic connective tissue with little glandular tissue. Meningoencephalitis.

Case 31, Jakob, 1923 (37): Female, 42. Emaciation, secondary anemia, premature menopause, falling of teeth. Skin parchment-like; no axillary, little pubic hair; speech slow; gait ataxic; Romberg positive; temperature 34.1 degrees

Centigrade. *Necropsy:* Fairly well developed fat pads. Capsule of hypophysis thickened; anterior lobe consisted only of fibrotic tissue, with no remains of normal glandular structure. Thyroid showed much connective tissue, small follicles, pale colloid.

Case 32, Jungmann, 1923 (38): Male, 44. Loss of appetite, weakness, headache, vomiting, great thirst. Sella turcica enlarged. Achylia gastrica with x-ray evidence of carcinoma of pylorus. Operation followed by death. *Necropsy:* Abscess of hypophysis, presumably metastatic, containing necrotic masses, but with some intact glandular tissue remaining. Suprarenals showed atrophy of cortex, strikingly thick capsule, but no marked sclerosis.

Cases 33, 34, 35, 36, and 37, Zondek, 1923 (39): Five cases, four of which were more or less typical of Simmonds' disease, and one of which showed obesity. Three females, one male, in one sex not stated. Anterior lobe of hypophysis was replaced by scar tissue in first four; in fifth, there was decrease in glandular substance of anterior lobe with much fibrous tissue, but in addition there were changes in the posterior lobe with destruction of its substance.

Case 38, Mueller, 1923 (40): Female, 59. Sudden death characterized by apoplectic features. Dry skin, sparse body hair, falling of axillary and pubic hair. *Necropsy:* Thyroid contained few very small follicles, otherwise connective tissue. Anterior lobe of hypophysis showed only sparse glandular rests; posterior lobe showed much connective tissue.

Case 39, Buday, 1923 (41): Sex not stated. Chronic weakness, secondary anemia, with simple atrophy of the endocrine organs. *Necropsy:* Gumma of hypophysis.

Case 40, Buday, 1923 (41): Sex not stated. Diabetes insipidus with loss of strength. *Necropsy:* Gumma of hypophysis.

Case 41, Budde, 1924 (42): Female, 27. Nine months before death, menopause. Operation. ? carcinoma of thyroid. Ophthalmoplegia, left. Falling of axillary and pubic hair. *Necropsy:* Tumor of hypophysis with metastases in lungs. Smallness of abdominal organs. Thyroid very small.

Case 42, Hirsch and Berberich, 1924 (43): Female, 57. Luetic. Between 30 and 40, loss of almost all teeth. At 40, loss of libido sexualis. At 52, menopause. At 53, loss of eye-brows, axillary and pubic hair. Slow, difficult speech. Weakness, fainting, chilly sensations, vomiting. No emaciation. Brown pigmentation of face. Basal metabolic rate 17 per cent below normal. Depression. Some improvement, especially of the psychic symptoms, on "Praephyson." *Necropsy:* Very small thyroid, with atrophic follicles. Anterior lobe of hypophysis transformed into almost homogeneous mass containing cholesterin crystals. Posterior lobe not altered.

Case 43, Lang, 1924 (44): Female, 38. Headache, cessation of menstruation, somnolence, vomiting, emaciation. *Necropsy:* Squamous cystopapilloma of infundibular region. Smallness of abdominal organs. Thyroid, ovaries, myocardium atrophic. Macroscopically and microscopically the hypophysis was not altered.

Case 44, Simons (45): (Literature not available).

Case 45, Graubner, 1925 (7): Female, 52. Between fortieth and fiftieth years, falling of teeth, four or five at a time. Marked rheumatic complaints. At 50, fainting, eight weeks in bed. Feeling of cold, swelling of legs and abdomen. Removal of great amounts of fluid by paracentesis. *Necropsy:* Generalized marasmus. Small, sclerotic hypophysis; capsule very much thickened; slight remnants of glandular tissue in anterior lobe. Generalized atrophy of the inner organs, particularly heart, liver, kidneys, suprarenals, genital organs.

Case 46, Cushing, 1925 (46): Middle-aged female. Sudden headaches followed by stupor, coma, death in three days. *Necropsy:* Pituitary adenoma with spontaneous hemorrhage, with complete intracapsular destruction of the gland.

Cases 47, 48, 49, Reye, 1926 (47): Reports histories of three women who became apathetic after delivery; syndrome suggestive of myxedema: low metabolism, white or yellowish skin, swollen face, loss of teeth, eyebrows and all hair on trunk and extremities, amenorrhea, low blood pressure and temperature, drowsiness and chilly feelings. No deaths.

Case 50, Pribam, 1927 (48): Female, 50. Septic puerperium at 31, at which time she was converted in a few weeks into an old woman, looking 50 or 60. Pubic and axillary hair fell out, also teeth. Periodic attacks of falling asleep, lasting about seven days, and occurring two or three times a year. At these times there were subnormal temperatures, very slow pulse, and blood pressure so low it could not be measured. Usually thyroid and supportive treatment would bring her out of the attacks, but she finally died in one of them. *Necropsy:* Complete destruction of hypophysis; complete fibrotic atrophy of thyroid; decrease in size of all abdominal organs.

Case 51, Tauber, 1927 (49): Female, 38. Weakness, apathy, subnormal temperature. No cachexia. *Necropsy:* Atrophy of anterior lobe of hypophysis.

Case 52, Suchier, 1927 (50): Female, with typical picture of Simmonds' disease. Treatment with "Praephyson."

Case 53, Reiche, 1927 (51): Female, 67. Weakness, emaciation, lack of body hair. *Necropsy:* High grade atrophy of anterior lobe of hypophysis. Syphilitic mesaortitis. Atrophy of thyroid.

Case 54, Ibotson, 1928 (52): Female. Deep pigmentation, asthenia, mental symptoms (delusions, delirium, etc.), vomiting. Feeding of whole gland pituitary (Burroughs-Wellcome tabloids) raised systolic blood pressure to 115; asthenia, mental symptoms, vomiting ceased; pigmentation not affected. Case observed 9 months; final outcome not stated.

Case 55, Thuer, 1928 (53): Female. Typical case of Simmonds' disease with pathological findings.

Case 56, Reye, 1928 (54): Female, 35. Difficult delivery, with marked loss of blood, long puerperium (without sepsis), cessation of menstruation, loss of libido, body weakness, pallor of skin, falling of hair and teeth, subnormal temperature, feelings of chilliness, gastro-intestinal disturbances, eosinophilia, low blood

pressure, low basal metabolic rate, cachexia. Completely relieved by treatment with "Praephyson."

Case 57, Herman, 1928 (55): Female, 53. Anorexia, falling of body hair, feelings of chilliness, loss of weight. Treated with good results with "Praephyson."

Cases 58, 59, 60, 61, Zondek and Koehler, 1928 (56): Four cases of emaciation, with tendency to water retention, lowering of sugar tolerance, low basal metabolic rate, low blood calcium, violent headaches, vomiting, motor unrest. Three females, one male. Good results in one case from insulin treatment. Feeding of pituitary products was without effect in any case.

Case 62, Altman, 1928 (57): Female, 48. Marked cachexia. Finally died of pulmonary tuberculosis. *Necropsy:* Hypophysis completely destroyed, with only a few remaining basophilic cells. Thyroid small. Spleen small. Marked atrophy of suprarenal cortex, with many small cells; suprarenal medulla normal.

Case 63, Frazier, 1929 (58): Male, 15. Headaches, vomiting, bowel movements sluggish, decrease in mental ability. Rough, dry skin. External genitalia underdeveloped. Thyroid not palpable. Loss of considerable weight. Blood sugar 54 mgm. per cent. Wassermann reaction positive in blood and spinal fluid. Operation for removal of cyst of cranio-pharyngeal duct. Post-operative course not satisfactory until "about five months after the operation . . . . there had been a striking improvement, which I presume must have been attributed to pituitary feeding."

Case 64, Timme, 1929 (59): Male, 20. Injury to head followed by emaciation and development of scleroderma. No necropsy.

Case 65, Herman, 1930 (60): Female, 48. Vomiting, nausea, weakness, loss of weight. Treatment with "Praephyson" and hydrochloric acid effected immediate and striking improvement.

Case 66, Stocks, 1930 (61): Female, 33. Symptoms of schizophrenia, extremely low weight, blood pressure estimated at 90 mm. mercury, subnormal temperature, subnormal basal metabolic rate. Treated with pituitrin with considerable improvement.

Case 67, Calder, 1931 (62): Male, 19. Weakness, anorexia, nausea, gaseous eructations, constipation, emaciation, loss of normal texture of skin, falling of axillary and pubic hair, decrease in libido and sexual power; subnormal temperature, low basal metabolic rate, low blood pressure. Marked improvement following treatment with a commercial acid extract of the anterior lobe of the hypophysis ("Antuitrin," Parke-Davis, Detroit, Michigan).

Case 68, Graham and Farquharson, 1931 (114): Female, 40. Admitted in coma. Eight years previously, following delivery, patient was acutely ill with fever, lower abdominal pain, and pain in chest. Slowly improved, but did not regain full strength. Axillary and pubic hair fell out, menstruation ceased, weight decreased, senility set in, patient lost interest in everything and was extremely sensitive to cold. Skin became dry and wrinkled, and teeth fell out. On admission, there was emaciation, absence of pubic and axillary hair, dry, wrinkled skin, low blood pressure (60 to 80 mm. systolic), temperature 103 degrees F., pulse 120, basal

metabolic rate 23 per cent below normal, blood sugar low (40 mgm. per cent). Patient still alive at time of report.

Case 69, Graham and Farquharson, 1931 (114): Male, 50. Onset two years previous to admission, with rapid gain in weight and loss of sexual desire and potency. This was followed by gradually progressing loss of weight and strength. Skin dry and scaly, hair gray and dry, abdominal viscera small, blood pressure 75 mm. Hg., systolic and 55 mm. Hg., diastolic. Basal metabolic rate 34 per cent below normal. Tendon reflexes hyperactive, Babinski reflex positive. Wassermann reaction in blood and spinal fluid positive. *Necropsy* showed atrophy and fibrosis of anterior lobe of hypophysis, with general atrophy of viscera. Impression was that patient had central nervous system lues with syphilitic fibrosis of anterior lobe of hypophysis.

Case 70, Graham and Farquharson, 1931 (114): Female, 38. Onset ten years before admission, following difficult labor. Weakness, emaciation, falling of axillary and pubic hair, irregular and scanty menstruation, difficulty in concentrating, sensations of coldness, wrinkling of skin, anemia, low blood pressure (80 mm. Hg., systolic), low basal metabolic rate (49 per cent below normal). "Antuitrin" (Parke-Davis) failed to effect improvement.

SYMPTOMATOLOGY

Perhaps the most striking and characteristic symptom of this disease is the emaciation that sooner or later develops in all these patients. In addition, there occur changes in the integument, including falling of the teeth and hair particularly in the axillary and pubic regions, trophic changes in the nails, and thickening and loss of luster of the skin, so marked at times as to resemble scleroderma. These changes combine to give to the patient the appearance of "premature senility." The patients are (at best) listless and apathetic; many of them display peculiar forms of pathological sleep; and in a not inconsiderable number coma precedes death. General muscular weakness is accompanied by corresponding atony of the gastro-intestinal tract, with marked constipation, vomiting, and a consequent distaste for food. Many of the case reports speak of subnormal temperature and feelings of chilliness. In all cases where it is reported, the basal metabolic rate has been considerably lower than normal, and the blood pressure is invariably low. The general slowing of all bodily processes, including general muscular debility, gastro-intestinal atony, vasomotor weakness, and decrease in the basal metabolic rate, present a striking similarity to the phenomenon of hibernation, which long has been considered to be under the control of the pituitary gland.

Without exception there occur changes in the sexual functions. In the female, menstruation ceases and as a consequence sterility ensues. In the male, there is sexual weakness amounting to complete impotence. In both sexes there is absence of sexual desire.

Zondek (56) stresses the occurrence of disturbances of salt and water metabolism, and maintains that the emaciation is the result of inability of the body to retain fluids; too few studies of this type have been made, however, to warrant inclusion of these findings among the symptomatology of the disease.

In a few cases psychic changes have been described, ranging from mild alterations of personality to gross delusions and delirious states. Whether these changes are actually a part of the syndrome described or merely an example of the deranged states frequently seen in chronic disease in general is not at all clear from the reports in the literature.

ETIOLOGY AND PATHOLOGICAL ANATOMY

Pathologically these cases have been characterized without exception by destruction of the anterior lobe of the hypophysis. In Simmonds' original case, the onset of symptoms coincided with puerperal sepsis, and although at the time of necropsy (eleven years after onset of the disease) the anterior lobe showed only scar tissue replacement, he assumed that the origin of the disturbance could be ascribed to bacterial emboli swept into this region at the time of the puerperal infection. The anatomical basis for such an assumption was elaborated by Simmonds (63) in 1914, when he pointed out that the arteries of the anterior lobe, in contradistinction to those in the posterior lobe, are end-arteries. Embolic processes in the hypophysis, he maintained, are not at all rare, and occur in both lobes; but whereas those in the posterior lobe give rise, if infected, only to small abscesses, those in the anterior lobe, producing necessarily infected anemic infarcts, result in marked destruction of tissue.

Influence of sex and pregnancy: Of the 70 cases reviewed, 47 occurred in females, 18 in males, and 5 in patients whose sex is not recorded in the case reports. Since females are affected much more frequently than males, it is important to determine whether pregnancy is of etiological significance in the production of this syndrome. Of the 47 cases occurring in females, 20 seem definitely to have developed as a result

of pregnancy, while in 18 of these cases, factors other than pregnancy seem to have initiated the process. The exact mechanism by which pregnancy causes insufficiency of the anterior lobe is not entirely clear. As mentioned above, Simmonds believes that emboli are responsible for the damage, but Reye (47) disagrees with this contention. He calls attention to the well known fact that during pregnancy the anterior lobe hypertrophies, only to undergo involution following delivery. He believes that in such an involuting organ the stage is set for the development of thromboses, and to such a pathological process, or perhaps to an excessive degree of the normal physiological involution of the gland, he ascribes the destruction of the anterior lobe and its ensuing dysfunction.

Almost half of the cases described in the literature have shown as the essential finding a destruction of glandular elements with replacement by scar tissue—the almost universal result of healed injury. Whether the original processes were, as Simmonds maintained, infected or uninfected emboli, or as Reye would have us believe, thromboses in an organ the victim of "super-involution," or simple atrophy as the result of intangible "toxins," or a part of a process of "multiple sclerosis of the endocrine glands," are questions to which answers subject to proof cannot be adduced; and indeed it is reasonable to suppose that no one pathological process has given rise to all the cases observed. Of suggestive significance is Simmonds' statement (22) that of 1700 consecutive necropsies in which the hypophysis was examined he found 17 cases of metastatic carcinoma, 9 cases of syphilis, 9 cases of tuberculosis, and 20 cases in which emboli were present in the hypophysis.

Tuberculosis: While according to reports in the literature tuberculosis is not an unusual disease of the hypophysis, its significance as a cause of destruction of the anterior lobe and hence of pituitary cachexia is less clear. In 1914, Simmonds (64) called attention to the relative frequency of tuberculosis of the hypophysis. He referred to Heidkamp's report of nine such cases, and to these added four cases which he had observed in less than a year. Of the cases of pituitary cachexia listed above, however, only that of Schlagenhaufer (21) seems certainly based on tuberculosis, while that of Schaeffer (26) showed granulation tissue that could have been either tuberculous or syphilitic in origin. Although the case of Claude and Gougerot (15) occurred in an individ-

ual dying of pulmonary tuberculosis, it is questionable whether tuberculosis was the cause of the changes in the hypophysis, and indeed whether the patient's disabilities were caused by pituitary insufficiency, for the symptoms of Simmonds' disease and those of chronic tuberculosis are in many respects the same.

Syphilis: Syphilis as a cause of hypophyseal destruction is likewise rare. Reye's case (27) is based only on clinical evidence; Reiche's case (51), showing high grade atrophy of the pituitary body, while occurring in a syphilitic individual, cannot with certainty be attributed to lues. The cases of Buday's (41) are said to have shown gummatous changes in the hypophysis, but his reports are too incomplete to be convincing.

Tumors: Redlich (115) has recently emphasized the fact that tumors and cysts may be of sufficient extent to cause the syndrome described. In this connection, a statement of Cushing's (46) is of interest:

". . . . though extensive operations for the removal of tumors such as the congenital lesions arising from the relics of Rathke's pouch are occasionally followed by a slow train of symptoms with fatality from inanition, I have never but once known of a clinical case in which the symptoms resembled the experimental cachexia hypophyseopriva which is so quickly fatal in animals. This case was that of a middle-aged woman who, while in normal health, had a sudden headache which was soon followed by stupor, coma and death in three days. . . . . Nothing whatever was found which could possibly account for the death but a small and unsuspected pituitary adenoma. Into this adenoma a spontaneous hemorrhage had occurred with complete intracapsular destruction of the gland."

Nine of the cases reviewed apparently were caused by tumors and cyst formation. In passing, it should be noted that tumors and cystic growths are frequently of such size as to press on neighboring structures other than the hypophysis, and hence the picture in such cases may be and often is distorted by symptoms referable not to pituitary disorder but to injury to adjacent structures.

Miscellaneous factors: Finally, as less frequent causes of destruction of the anterior lobe, von Monakow's case (33) of acute inflammation and Reinhardt's (35) and Timme's (59) cases of fracture of the base of the skull may be mentioned.

Changes in organs other than the hypophysis: The changes in the integument, thickening and loss of luster of the skin, falling of the hair

and teeth, and trophic changes in the nails, have already been mentioned. Conspicuous changes occur in other glands of internal secretion: macroscopically, the thyroid, parathyroid, suprarenal cortex, and reproductive glands are markedly decreased in size, and microscopically this decrease in size is seen to be due to an actual atrophy of the glandular structure. In addition, there are regressive changes in all of the abdominal viscera, so that the liver, spleen, kidneys, and pancreas are much smaller than normal. To emphasize the etiological importance of pituitary insufficiency in this condition Simmonds has used the term "Splanchnomikrie," in contrast in the splanchnomegaly which accompanies over-functioning of this gland.

PATHOLOGICAL PHYSIOLOGY

In order to interpret the symptomatology of any endocrine disturbance, it is necessary to remember that the glands of internal secretion are mutually interdependent, and that injury to one may lead to secondary changes, functional or anatomical, in others. The endocrine system, moreover, consists of a series of checks and balances, of pressors and depressors, the proper coördination of which is necessary for normal hormonal activity; and it therefore follows that symptoms may be produced not only by the absence of a given hormone but perhaps also by the release of a second hormone to which the first is normally antagonistic.

These circumstances make the untangling of any endocrine syndrome difficult, and, although some of the symptoms may be explained with a fair degree of certainty, there remain many gaps in our knowledge. Especially is the symptomatology of cases of pituitary insufficiency difficult of interpretation, for the anterior lobe elaborates not a single, easily isolated principle, but at least two, perhaps more, hormones, having a wide variety of physiological effects. Thus Bugbee, Simond and Grimes (65), in a recent review of the literature on the work of the anterior pituitary, list eleven separate effects of various extracts of this structure. That each of these effects is due to a separate hormone is, of course, unlikely; but that there are at least two hormones seems well established by experimental work (66). As reported by Evans and Simpson (67), in 1929, these are: (*a*) a growth-promoting hormone, elaborated presumably by the eosinophilic cells of the

hypophysis and present principally in alkaline extracts; and (*b*) a gonad, thyroid, suprarenal-cortex activating hormone produced by the basophilic cells and present mainly in acid extracts. Moreover, these two factors seem to be somewhat antagonistic, for an excess of one is said to depress the action of the other.

In order properly to interpret the disease syndrome presented by patients with Simmonds' disease, a consideration of the effects of these hormones on other endocrine glands is indispensable.

Anterior pituitary and thyroid: Much experimental work has been done to confirm the assumption that there exists between hypophysis and thyroid a very close relationship. This relation is particularly evident in the case of amphibian larvae, in which, after removal of the hypophysis, the thyroid remains very small (68, 69) and presumably functionless, for metamorphosis fails to set in unless thyroid extract is administered (70). Disabilities induced by removal of the pars glandularis of the hypophysis are corrected by transplants of similar glandular substance obtained from frogs (71). Confirmatory results have been obtained by Uhlenhuth and Schwartzbach (72) in the case of salamanders. Moreover, there is a reciprocal effect of thyroid on hypophysis, for according to Hoskins (73) after thyroidectomy the hypophysis becomes larger, and according to Kahn (74) after feeding of thyroid it becomes smaller.

So far as warm blood animals are concerned, early experimental results were conflicting. It is accepted by most writers (75, 76) that after removal of the thyroid the hypophysis increases in size, the most pronounced changes being in the various cellular elements of the anterior lobe. The effect of thyroidectomy on the hypophysis has been particularly studied by Tomozawa (77), who showed that following thyroidectomy the acidophiles of the anterior hypophysis first decrease and then gradually increase in size, number, and evidence of functional activity to reach a maximum about seventy days following the operation. He interprets this increase as being compensatory in nature.

An excess of the anterior lobe substance causes, among other things, enlargement of the thyroid. Benedict, Putnam, and Teel (78), for example, have recently shown that the injection of alkaline extracts of the anterior pituitary in dogs causes hypertrophy of the thyroid, an effect that has a clinical counterpart in acromegaly. Loeb and Bassett

(79) have shown that subcutaneous injection of either acid or alkaline extracts will cause marked hypertrophy in the thyroid of guinea-pigs, the changes resembling those of Graves' disease. Crew and Wiesner (80) have attempted to prove that the hormone involved in all these reactions is separate from the growth-promoting and gonad-stimulating hormones of the anterior pituitary, but the question is still open. The effect of the urine of pregnant women on the thyroid apparently has not been studied.

P. E. Smith (13) has given us the most conclusive experimental work on the relation between the two glands. He showed that one of the results of removal of the anterior pituitary was a decrease in weight of the thyroid, and that histologically there was marked flattening of the thyroid epithelium. Moreover, that this decrease in size of the thyroid was actually due to pituitary insufficiency was proved by the fact that transplants of pituitary induced reparative phenomena in the thyroid so that it appeared structurally normal. Smith (81) further showed that this anatomical decrease in the thyroid was accompanied by a corresponding functional decrease, the basal metabolic rate of totally hypophysectomized rats being about 35 per cent below the average. That the low basal metabolic rate is actually due to anterior pituitary insufficiency is indicated by the facts that the fall in basal metabolic rate does not take place after removal of the posterior lobe alone, and that the low basal rate following total hypophysectomy is restored to normal limits by treatment with anterior lobe but not with posterior lobe transplants. Smith also says:

". . . . we do not wish to indicate that our conclusions are that anterior pituitary in itself, as appears to be the case with thyroid, can stimulate the metabolic rate. . . . . The low metabolic rate displayed by the hypophysectomized rat may be directly due . . . . to a deficiency in the secretion of one of the other endocrine glands; the rise in the metabolic rate with anterior pituitary transplants may be due to the functional repair of this other gland. That such is probable is suggested by the fact that thyroid administration raises the metabolic rate in hypophysectomized animals."

Smith and others (82) later supplemented these reports by showing that administration of thyroid to hypophysectomized animals would raise the basal metabolic rate but that it could not alter the stunted growth of such animals nor restore the suprarenals, thyroid, or genital systems, which had atrophied as the resulted of pituitary ablation.

In the above series of facts, then, we have experimental explanation of many clinical findings: Thus, as is well recognized, and as was recently emphasized by Liebesny (83), acromegalics, in whom there is a hyper-functioning of the anterior lobe, frequently show an enlarged thyroid and heightened basal metabolic rate. Hypophyseal dwarfs, on the hand, show, as described by Simmonds (84), hypoplasia of the thyroid and a low basal metabolic rate. And finally, the experimental facts cited furnish a logical basis for the low basal metabolic rate observed in cases of Simmonds' disease, and indicate that while in certain of these cases thyroid extract may be necessary, it is futile to expect relief of all the symptoms of this disease by thyroid administration alone. The question is also raised as to whether certain cases of hypothyroidism, notably cretinism, might not be due to pituitary insufficiency and hence need a supply of the anterior lobe hormones to effect alleviation of the symptoms.

Anterior pituitary and suprarenal cortex: Many of the symptoms of Simmonds' disease, notably the low blood pressure, subnormal temperature, weakness (both generalized and gastro-intestinal), and trophic changes in skin and nails, resemble those of Addison's disease. The two disease conditions differ mainly in that pigmentation of the skin is present in the one and not in the other, although Ghrist and Rowntree (85), among others, have reported cases of Addison's disease in which necropsy showed tuberculosis of the suprarenals but in which there was no pigmentation. The question whether the symptoms of hypotension and asthenia observed in Simmonds' disease are attributable directly to pituitary insufficiency or to secondary involvement of the suprarenal cortex is, therefore, a pertinent one. Unfortunately, in the cases reported in the literature the therapeutic test was not available, for the specific hormone of the suprarenal cortex has only recently been isolated by Hartmann (86) and by Swingle and Pfiffner (87). Necropsy findings and experimental evidence show, however, an intimate relation between the anterior pituitary and the suprarenal cortex. Thus, Moehlig (88) has reviewed the literature on anencephaly and has pointed out that in this condition, in which there is of course an absence of the pituitary body, the suprarenal cortex is hypoplastic.

Kraus (89), in a very interesting study of the pathology of Addison's disease, has pointed out that in those cases of Addison's disease

dependent on tuberculosis of the suprarenals there are few, if any, changes in the hypophysis. On the other hand, he describes four cases of "Addison's disease" dependent on "sclerosis of the suprarenal cortex" in which the anterior lobe, particularly the basophilic elements, showed marked evidences of degenerative processes. These changes he considered to be secondary to suprarenal insufficiency, but in the light of evidence now available it seems much more logical to assume that the changes in the pituitary were primary. Fourteen cases with similar findings are recorded by Blasek (90), who further quotes Fahr and Reiche as having collected eighteen cases of "Addison's disease" dependent on idiopathic atrophy of the suprarenal cortex. Two such cases were reported by Medlar (91), who quotes Bittorf's finding forty-seven others.

On the experimental side we have the facts that removal of the pars glandularis causes the suprarenals of tadpoles to remain abnormally small, while the under-development is repaired by transplants of anterior pituitary obtained from frogs (69, 92). Ascoli and Legnani (93) observed in dogs, and Smith and co-workers (13) in rats, that destruction of the hypophysis resulted in an atrophy of the suprarenal cortex. Conversely, according to Evans, administration of anterior lobe extract to rats leads to hypertrophy of the suprarenal cortex.

In the light of these experimental facts the hypertrophy of the suprarenal cortex in acromegaly and its small size in Simmonds' disease become intelligible. Moreover, one can hardly escape the interpretation that cases of "Addison's disease" such as those mentioned above as being due to idiopathic sclerosis of the suprarenal cortex are not due primarily to disease of the suprarenals but to atrophy and underfunctioning as a secondary effect of anterior pituitary insufficiency.

Anterior pituitary and island cells of the pancreas: It was of interest to note in a case that we recently observed (62) that before treatment the patient showed a type of sugar tolerance curve characteristic of mild diabetes and that on two occasions he showed small amounts of sugar in the urine; after treatment the sugar tolerance curve became normal and glycosuria disappeared. Other clinical reports in the literature are silent on this point, and whether the diabetic type of response to the ingestion of glucose is the rule in such cases we do not know. Moreover, necropsy findings for the most part make no men-

tion of the microscopic condition of the pancreas, though many indicate that this organ was reduced in weight.

Observations, both clinical and experimental, concerning the relation of the pituitary to the islands of Langerhans have been reviewed extensively in a recent article by Colwell (94). Clinically we have the important facts: (*a*) that acromegaly is frequently accompanied by diabetes; (*b*) that this diabetes is usually comparatively mild; (*c*) that it ordinarily develops some time after the symptoms of acromegaly have become well established; and (*d*) that while changes in the pancreas in cases of acromegaly and diabetes have been found only in a "limited number" of cases, the change most frequently observed has been sclerosis and atrophy of the islands.

Colwell quotes Fry's (95) findings, confirmed by Kraus (96), that cases of ordinary diabetes studied showed changes in the anterior lobe in the nature of adenomatous masses of eosinophilic cells, excess of colloid, and areas of cellular degeneration. It must be admitted, however, that adenomatous masses of microscopic size are not uncommon in normal hypophyses.

Due to the fact that until recently operative procedure on the pituitary body in experimental animals has been almost impossible without coincident injury to adjacent structures, experimental evidence concerning the rôle of the hypophysis in diabetes has been more confusing than helpful in interpreting the clinical observations. The occurrence of mild diabetes in the case mentioned above raises the question whether hyperglycemia and glycosuria may arise as the result of an insufficiency of some element elaborated by the anterior pituitary. That the diabetes of acromegaly may be due to pituitary insufficiency, paradoxical though the idea may seem at first, is not at all impossible, for not only may the basophilic cells (endocrine-stimulating) be structurally compressed by the expanding eosinophilic adenoma of acromegaly, but the additional possiblity exists that the over-production of the acidophilic secretion, being antagonistic to the endocrine-stimulating hormone, may result in a physiological insufficiency of the latter and thus lead to functional incompetence of the islet cells of the pancreas.

These hypotheses are not presented as explanations but rather as an indication of certain important physiological problems that remain to be attacked from an experimental standpoint. Pending such crucial

experiments, the entire question of the relationship of anterior pituitary to islet cells must remain open.

Anterior pituitary and reproductive glands: It is of considerable significance that almost without exception the cases reported in the above series were marked, in the case of the female, by cessation of menstruation, and in the case of both male and female by impotence and loss of libido sexualis. Extensive work during the past few years has furnished a well founded experimental basis for these phenomena. Thus Smith (13, 97) showed in 1927 that ablation of the anterior pituitary in rats led to atrophy of the genital system with loss of libido sexualis and in the female to an immediate cessation of the sex cycle. If the hypophysectomy took place before ovulation, there would be present in the ovaries interstitial tissue, normal primordial follicles, degenerating small follicles, and no corpora lutea. In the sexually mature animal, the ovarian picture was the same as in the immature rat except for the corpora lutea, which persisted for weeks after the operation. Investigation of the effects of replacement therapy showed that fresh, living hypophyseal transplants administered daily invariably caused oestrus in the female after a lapse of from five to seven days, the uterus changing from its atrophic, threadlike, pale appearance to the oestrual type. The ovaries became as large or larger than normal, and showed many follicles and corpora lutea. In the male, the testes, which invariably atrophied following hypophysectomy, would after treatment become normal in size and differ in no way from those of the unoperated control. The males would mate and normal litters result, whereas previous to the treatment they displayed no interest in the oestrous female.

Zondek and Aschheim (98), Johns (99), and Smith and Engle (100) subsequently adduced further evidence of the intimate relationship between pituitary and sex apparatus by a series of experiments in which they transplanted anterior pituitary substance into immature female rats or mice and secured thereby precocious sexual development, with formation of many ovarian follicles, super-ovulation, enlargement of the uterus and opening of the vagina with cornification of its epithelium. That these changes were the result of interaction between anterior pituitary and the ovary was indicated further by the fact that these changes did not occur if ovariectomy had preceded the

transplantation of the pituitary substance; but thyroid and suprarenals apparently were not concerned, for the changes took place even after removal of these glands. Evans and Simpson (101) have shown that the response of the ovaries to anterior pituitary transplants is proportional to the amount of tissue implanted and that the increase in size is due to the formation of follicles.

Similar results were obtained in monkeys by Allen (102), who found that following a series of transplants of the anterior pituitary there was within seven days a marked development of secondary sexual characteristics, considerable growth of the genital tract and mammary glands, enlargement of the ovaries, and follicle formation.

That the hypophysis and gonads function reciprocally in inducing sexual maturity is indicated by the work of Engle (103), who found that the ovarian response (follicle formation) to anterior pituitary transplants obtained from gonadectomized animals was significantly greater than to transplants obtained from normal animals, and further that after gonadectomy the basophilic cells of the anterior lobe are increased in number and size and that they become vacuolated. These facts he interprets as indications of storage of the maturity-inducing substance in the hypophysis, and deduces that the secretion of the gonads therefore constitutes a "release mechanism" without whose influence the hypophysis will not give up this hormone. Evans and Simpson (104) believe that this "releasing substance" is elaborated by the germ cells themselves and not by the interstitial cells, since hypophyseal transplants from cryptorchid males are less effective in provoking precocious sexual maturity than are similar transplants from castrated males. It is of some interest to note that although the female hypophysis is invariably larger than the male hypophysis, the latter is much more potent than the former in inducing sexual maturity (105).

Not only can the changes described above be produced by transplants and extracts of the anterior pituitary, but some of them at least can be produced by the blood serum or urine of pregnant women. Thus it was discovered in 1928 by Aschheim and Zondek (106) that the urine from pregnant women was capable of inducing precocious sexual maturity in mice, and this fact has become the basis of the now well known and widely used Aschheim-Zondek test for pregnancy. But the hormone so obtained differs in its effect from pituitary transplants

and extracts particularly in that, whereas the latter cause follicle formation and super-ovulation, the former causes conspicuous luteinization of the partially matured follicles, as has been pointed out by Smith and Engle and by Evans and Simpson. There thus are seen to be two different effects, follicle formation and luteinization. Whether these two effects are dependent on two separate hormones or represent varying expressions of the same principle is yet to be determined.

Finally, as a most significant pituitary-gonadal relationship must be mentioned the epoch-making work of Hartman, Firor, and Geiling (107), namely that in addition to the follicle-stimulating and luteinizing effects, the anterior pituitary also produces a hormone which, activated apparently by the Allen-Doisy hormone (theelin), initiates uterine bleeding of menstruation.

While the great bulk of work dealing with hypophysis-gonadal relationships, as outlined above, has been done on females, experiments with males have shown that the relationship here is just as intimate and striking. Thus, according to Smith and Engle (100), hypophysectomy is followed in the male by decrease in the size of the penis and testes, and replacement therapy is followed, apparently through mediation of the testes, by increase in size of the penis and accessory organs. Steinach and Kun's (108) more extensive experiments have indicated the same effects: Injections of anterior lobe extracts into infantile male rats were followed by descensus of the testicle (or, in animals in which descensus had already occurred, by enlargement of the testicle), hyperemia and protrusion of the scrotal skin and development of the penis and preputial tube (corpus cavernosum and glans penis), seminal vesicles and prostatic glands of mature form, marked increase in Leydig's interstitial cells of the testicles, erotization, libido, and mating power. Similar changes were produced in eunuchoid males and in senile male rats, though larger doses were required. Regressive changes ensued when the injections were discontinued. (For a review of this work in English, see Benjamin (109).)

Experiments concerning the effect of urine from pregnant women on the male are few. Engle (110) found that such injections into immature male rats caused a marked hypertrophy of the sex apparatus, with the exception of the testis. There was marked increase in the interstitial cell masses, but no acceleration of spermatogenesis. Varying degrees of destruction of the seminal vesicles often occurred.

In view of these experimental facts, it is not surprising that cases of Simmonds' disease show both anatomical and functional changes in the sex apparatus. That milder disturbances of the sexual functions may be dependent on pituitary insufficiency seems highly probable. Clinical application of the principles established by investigative work, however, is now only in the experimental stage, and a review of the literature on the subject is hardly germane to our present discussion.

Relationship of Simmonds' disease to the so-called "pluriglandular syndromes:" The literature abounds in reports of cases showing symptoms referable to several of the glands of internal secretion. Thus Barker (111) speaks of a thyreo-testicular-hypophyseal-suprarenal syndrome, which he says affects males between 25 and 45, and results in loss of hair, indigestion, emaciation, sallow tint to the skin, subnormal development of the genitalia, chilliness, and hypotension. Necropsy, according to reports in the literature, has usually shown in these cases sclerosis of the various endocrine organs, and attempts have been made to establish such a condition as a clinical entity. To do so, however, necessitates the postulating of some toxin, chemical or infectious, that will have a selective, deleterious effect on these structures, or, equally unsatisfactory as an explanation, the assumption that there is present in these individuals some "diathesis" or "constitutional inferiority" that makes them susceptible to multiple glandular defects.

In the light of the close agreement between clinical picture, necropsy findings, and experimental results, all of which show atrophy and fibrous tissue replacement of the endocrine glands as a result of insufficiency of the anterior lobe of the pituitary, such explanations seem labored and unnecessary, and it seems logical to agree with Simmonds' original contention, that the hypophysis is primarily at fault and that the other changes, including decrease in size and function of the endocrines, are secondary in nature, even though symptoms referable to these secondarily affected structures may form the most conspicuous part of the picture.

Relationship of pituitary to higher nervous centers: Numerous attempts have been made to correlate the work of the pituitary with higher centers, particularly with those in the region of the hypothalamus, and indeed the intimate juxtaposition of pituitary with the central nervous system seems hardly to be accidental. Of the references

cited, those of Jakobs (37) and of Zondek (56) stress particularly such relationships. It is often stated that in the hypothalamus are located many important centers, notably those having to do with temperature regulation, sugar metabolism, perhaps salt and water metabolism, specific dynamic action, and even vasomotor control; but whether the pituitary body exercises any control over these centers, or *vice versa*, is far from clear.

Of the clinical observations, only that of Lang (44) appears to be of significance: He reports a case simulating Simmonds' disease both symptomatically and anatomically, in which at necropsy there was found a cystic tumor of the infundibular region without any evidence of pituitary destruction. Such an observation is, of course, suggestive, as is the intimate anatomical relationship of the pituitary to the central nervous system; but there exists no clear-cut experimental work defining the functional connection between this gland and higher centers, and it would seem wise, therefore, to leave the matter open.

TREATMENT

Inasmuch as the primary destructive factors responsible for injury to the anterior lobe are, for the most part, not subject to therapeutic attack, our efforts must be concerned with supplying the missing hormone. Experimentally, as has been mentioned, Smith (13, 97) has been able by the use of transplants and extracts to effect repair of most of the disabilities incident to pituitary removal, and has thereby established the rationale of therapeusis in these cases.

Reye (47, 54) seems the first to have succeeded in producing clinical improvement. He used an anterior lobe extract, "Praephyson," marketed by Passek and Wolf, Hamburg, the exact nature of which is not indicated in his reports. Improvement, according to his accounts, was so striking that he proposed use of this material as a diagnostic procedure in a suspected case.

In a case which has come under our observation, improvement followed the use of "Antuitrin," an acid extract of the anterior lobe prepared by Parke-Davis, the material being given hypodermically in daily doses of 1 cc. Although good results were obtained under this treatment, it cannot be concluded that every sample of this material will be found potent. As a matter of fact, recent experimental work

on the subject points to the unstable character of these extracts, and no doubt much work remains to be done before stable preparations are available for clinical application. In the absence of adequate methods of biological assay of potency, it must be considered a fortunate accident that a fresh and potent supply of the required hormone was available for our case.

It is important to know whether similar results are to be expected from oral administration of these extracts. Numerous experiments aimed at the production of acromegaly by feeding anterior lobe substance have been failures. Smith (112) found that the daily feeding of fresh bovine anterior pituitary glands to experimental animals does not cause any increase in body weight, nor does it restore, in the slightest degree, the atrophied genital system, thyroids, or suprarenal cortex of the hypophysectomized rat. The clinical implication is obvious.

Whether extracts of other glands, notably the thyroid, may be required to supplement the pituitary extracts, depends most likely on the duration of the disease. Thus, it is reasonable to assume that in the early stages the insufficiency of the thyroid rests on a functional basis, and accordingly supplying the missing pituitary hormone should re-activate the structurally competent thyroid. Such a state of affairs seemed to exist in our case. That the thyroid, if not permanently damaged, may be stimulated by injections of anterior lobe extract is further indicated in a case recently studied by Dr. Jean Craven (113) of this hospital: The patient was a girl of 12 presenting signs of pituitary gigantism, whose basal metabolic rate was raised from 2 per cent below normal to 33 per cent above normal by the use of "Antuitrin." If, on the other hand, the disease has endured for a long time, then anatomical changes of the nature of disuse atrophy will have set in, and in such event it is reasonable to assume that not only the pituitary hormone but also those of the secondarily involved glands may be required in order to relieve the symptoms.

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THE NATURE OF ALLERGY IN TUBERCULOSIS AS REVEALED BY TISSUE CULTURE STUDIES[1]

ARNOLD RICE RICH AND MARGARET REED LEWIS

From the Department of Pathology of the Johns Hopkins Medical School, Baltimore, and the Department of Embryology of the Carnegie Institute of Washington

When a foreign protein, whether bacterial or non-bacterial, finds its way parenterally into the animal body, certain changes take place in the body as a result of contact with that protein. The exact nature of these changes is still obscure, but the effects which they may produce if the same protein reaches the tissues again are quite familiar in the guise of the various "hypersensitive reactions" to foreign protein. Depending upon conditions the reaction may appear in the form of anaphylactic shock, asthma, hay fever, serum sickness, "food allergy," the Arthus phenomenon, or the tuberculin and other similar reactions to the proteins of bacteria. While these various conditions appear at first sight to be very different from each other, there is persuasive evidence that underlying all of them is the fundamental circumstance that the exposure of the tissues to a bland, undigested foreign protein stimulates the production of a specific antibody, different for each protein, which has the power of reacting with the protein in some way, and that the different forms of hypersensitive reaction are results of the interaction of antibody and protein antigen under different conditions.

If the various above-mentioned forms of hypersensitivity, which may appear superficially to be very different one from the other, are examined more closely it will be found possible to separate them all into two distinct groups. In the first group may be placed those cases in which contact with the foreign protein to which the body has been sensitized leads especially to symptoms which result from the spasmodic contraction of smooth muscle fibres, particularly the fibres of the bronchial or vascular musculature. In the second group, contact with the same protein produces local damage or death of

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tissue accompanied by acute inflammation. In both groups general constitutional symptoms and even death may occur, in addition to the more local manifestations, if the protein to which the body has developed an antibody finds its way into the blood stream in sufficient quantity under proper conditions. It may be that this grouping of hypersensitive reactions is essentially artificial as far as the underlying mechanism is concerned, for it is quite possible that an identical form of antibody-antigen interaction may be responsible for both of these objectively different manifestations of hypersensitiveness; but the terms "allergy" and "anaphylaxis" have been so loosely used to designate all sorts of states of altered reactivity that, for the purpose of clarity, we have found it convenient to restrict the term "anaphylactic" to the muscle-spasmodic type of reaction, and the term "allergic" to reactions of the inflammatory-necrotizing type (1), and it is in this sense that these two terms will be used in the present paper.

Although there is good reason to believe that the allergic inflammatory-necrotizing reaction and the anaphylactic musculo-spasmodic reaction are both the results of the interaction of antibody with antigen, and although an animal may be made both allergic and anaphylactic to the same protein, nevertheless it was shown some time ago by Baldwin (2), Zinsser (3) and others, that allergy may exist without anaphylaxis and *vice versa*. The tissues of a particular tuberculous animal, for example, may become inflamed and undergo necrosis on contact with tuberculoprotein (allergy), and yet its smooth muscle may exhibit no tendency to be thrown into contraction (anaphylaxis) when properly exposed to this protein. Another animal may develop both the inflammatory-necrotizing tendency and the musculo-spasmodic type of sensitivity; and a third, by proper treatment, may be made to develop the tendency to smooth-muscle spasm on contact with tuberculoprotein without developing any susceptibility on the part of the tissues in general to that damaging effect of the protein which is characteristic of allergy. In spite of all this, we repeat that it remains quite possible that both allergy and anaphylaxis may be merely different manifestations of an identical antibody-antigen reaction developing and occurring under different conditions.

That the anaphylactic state depends upon the production of an antibody, specific for the particular protein introduced, has been clear ever since the demonstration that anaphylactic hypersensitivity can be transferred passively to a normal animal by injecting into it the serum of an anaphylactic one. Furthermore, it seems clear that the anaphylactic reaction must be a result of the interaction of this antibody with some part of the protein antigen, since a mixture of the serum of an anaphylactic animal with the protein to which that animal is sensitized may produce anaphylactic shock if injected into a normal animal. Although such experiments leave no doubt as to the presence of a specific antibody in the circulating blood of an anaphylactic animal, many other experiments make it appear that this *circulating* portion of antibody is not necessary for the spasm of smooth muscle characteristic of the anaphylactic reaction. For example, a strip of smooth muscle from an anaphylactic animal, which has been thoroughly perfused in order to wash it free from plasma, will still exhibit the characteristic anaphylactic contraction *in vitro* on contact with the specific protein. It therefore appears that, in anaphylaxis, an effective amount of antibody is attached directly to the smooth muscle fibres, and that in addition a residual amount circulates freely in the blood.

In the case of allergy the state of affairs is not quite so clear. In the Arthus phenomenon (the allergic, necrotizing-inflammatory, tuberculin type of reaction produced by the injection of a protein, say egg albumen, into the skin of an animal sensitized by previous injections of that protein) it is plain that we are dealing with an antibody-antigen reaction, and that at least part of the specific antibody is free in the circulation, for the allergic sensitivity to egg albumen can be passively transferred to normal animals by the injection of the serum of an animal capable of exhibiting the Arthus phenomenon as a response to that protein; and the beautiful studies of Opie (4) have shown that, if egg albumen be mixed with the serum of such an animal, a precipitate forms which will produce inflammation and necrosis when injected into the skin of a normal animal. It is not yet known, however, whether any antibody is bound to the tissue cells of the animal susceptible to the Arthus phenomenon, as it is in the case of anaphylaxis; and when we turn to the allergic state which develops during the course of so many bacterial infections our information becomes so meagre that it is only

through reasoning from analogy that we can even suggest that an antibody-antigen reaction takes place; for in contrast to the ease of demonstrating circulating antibody in the case of the Arthus phenomenon in which the body is artificially sensitized to a foreign protein, all attempts to detect, by the method of passive transfer, a circulating antibody responsible for the allergy arising during bacterial infection have been inconclusive to say the least, and no one, as far as we know, has previously attempted to determine whether the isolated tissues of the allergic body, when freed from nervous and circulatory influences, are sensitive to the action of the particular bacterial protein to which the body has become allergic through infection. It was the purpose of the present investigation, of which we have published a brief preliminary note (8), to attempt to acquire information regarding this matter. A similar study of the Arthus phenomenon will be reported later.

It is perfectly clear that, during the progress of infection with the tubercle bacillus, the body becomes changed in some way which renders the relatively bland protein of the bacillus capable of acting upon its tissues as a violent, necrotizing poison (1). In just what this change consists is not clear, but one can hardly resist the belief that the change is of the same general nature as that which, in the case of the Arthus phenomenon, renders such a harmless protein as egg albumen capable of producing violent inflammation and extensive necrosis. However, as we have said, allergy in tuberculosis differs from the allergic Arthus phenomenon in that it has not been successfully transferred passively. Furthermore, whereas Opie (4) was able to show that the mixture of egg albumen with serum from an animal sensitized to that protein resulted in the formation of an irritant capable of producing necrosis when injected into normal tissues, neither Zinsser (6) nor Rich and McCordock (7) were able to demonstrate the formation of a noxious substance when the serum of allergic, tuberculous animals was mixed with tuberculoprotein. What then is the nature of allergy in tuberculosis, since all attempts to demonstrate the existence of a circulating antibody have been unsuccessful or equivocal? There are several obvious possibilities. It may be that there is in the plasma of the allergic animal an antibody capable of interacting with tuberculoprotein to produce a substance toxic for cells, but that the methods used to demonstrate it have heretofore been inadequate. It may be

that the antibody has become attached to the tissue cells as the anaphylactic antibody is attached to the smooth muscle cells but that, unlike what happens in anaphylaxis, no appreciable surplus of antibody remains in the circulating blood. It may be that there is an antibody in the plasma of the allergic body of such a nature that its interaction with tuberculoprotein leads to the formation of a substance which is noxious only to the cells of the allergic body which may themselves be altered in some way; in such an event it would obviously be impossible to demonstrate the presence of the antibody by passive transfer to normal animals. Finally, it may be that the occurrence of allergic damage to tissues depends upon nervous or circulatory influences independent of any inherent alteration of the tissue cells at the site of the reaction.

Since, in the analysis of similar problems in the case of anaphylaxis, the *in vitro* attack in which the reactions of isolated strips of smooth muscle are studied has yielded such fundamental information, it seemed desirable to try to apply to allergy the method of study of isolated tissues. For this purpose the method of tissue culture seemed particularly suitable, for cells under the conditions of tissue culture are delicate indicators of the presence of cytotoxic substances, they are free from all complicating nervous and circulatory influences, and the study of free cells is by far the most satisfactory method of deciding such questions as whether the cells of the allergic body will be damaged by tuberculoprotein in the absence of allergic plasma. Another important advantage of the method of tissue culture in the study of the problem of allergy is the fact that it eliminates the uncontrollable differences in the local concentration of antigen which occur in the intact body. It has been shown by Opie (5) that a foreign protein to which the body is sensitized is held fixed at the site at which it is injected, whereas in the normal non-allergic body it diffuses from the site more rapidly. In tissue culture, the tuberculoprotein added to the drop of plasma in which the cells are placed cannot escape or suffer uncontrollable dilution and the migrating cells, whether normal or allergic, must therefore wander out into a medium containing in each case the same concentration of the antigen.

It is clear that in tissue culture the washed cells and the plasma of allergic and of non-allergic animals can be brought together with tuber-

culoprotein in all of the various combinations which are capable of yielding information regarding the possibilities which we have outlined above. The most important combinations for this purpose are:

1. Washed cells of allergic body + plasma of allergic body + tuberculoprotein.
2. Washed cells of allergic body + plasma of normal body + tuberculoprotein.
3. Washed cells of normal body + plasma of allergic body + tuberculoprotein.
4. Adequate control combinations to be described below.

The first of these combinations represents the reproduction *in vitro* of the basic conditions of the allergic reaction, and it follows that if the cells are damaged or killed by the tuberculoprotein in such cultures, nervous, circulatory or other mechanisms dependent upon the intact body are unnecessary for allergic damage to tissues.

If the cells are damaged by the tuberculoprotein in the second combination in which the plasma of the allergic body is excluded, it is evident that the cells themselves are altered in such a way (whether internally or by absorption of antibody) that tuberculoprotein acts directly upon them as a poison, and that circulating antibody is not necessary for the immediate damage.

Finally, if the normal cells in the third combination are damaged, it is clear that the plasma of the allergic body contains an antibody which acts upon tuberculoprotein to produce a noxious substance which is capable of damaging cells in general.

EXPERIMENTAL METHOD

Well grown guinea-pigs were each given 0.5 cc. of a heavy suspension of avirulent human tubercle bacilli (R 1) subcutaneously. After the lapse of several weeks they were tested by the intracutaneous injection of tuberculin. Those reacting with necrosis to 5 mg. of O.T. were used as the allergic animals in the experiments. Ordinarily, an interval of several days to a week was allowed to elapse between the skin test and the experiment.

The routine of the experiments was as follows: Blood was drawn from a normal, non-allergic guinea-pig and from an allergic one into separate syringes containing a small amount of a solution of heparin. The contents of the syringes were delivered into centrifuge tubes which

were at once sealed with parafined paper, placed in centrifuge cups containing ice, and centrifugalized at high speed until the cells were well sedimented. The supernatant plasma from each guinea-pig was drawn off with a pipette and placed in a small covered dish. If the cells of the buffy coat were to be studied, this layer was lifted off each specimen and placed in separate dishes containing Locke's solution. It was then, in each instance, cut into very small pieces (1 mm. or less in diameter) and the little pieces were picked out with a capillary pipette and transferred to a second dish containing 10 cc. of Locke's solution in which the pieces were washed by being shaken about. They were again picked up with a capillary pipette and transferred to fresh Locke's solution and washed again. This was repeated, so that the fragments of buffy coat were thoroughly washed through three changes of Locke's solution of 10 cc. each. Each time care was taken to avoid, as far as possible, taking up the surrounding fluid with the bits of buffy coat when they were being transferred to a fresh bath of Locke's solution. All manipulations were, of course, carried out under strict aseptic precautions. When splenic tissue was used, the animal was opened aseptically after having been bled, and a small piece of spleen was removed with sterile instruments. This was cut in Locke's solution into minute fragments and washed as above.

While the cells were being washed in this manner the dilutions of tuberculin in plasma were being prepared. It required at the beginning some experimentation to determine the optimal concentration of tuberculin. With the tuberculins at our disposal, which were kindly furnished to us by Dr. H. S. Willis and were of excellent quality, the most satisfactory concentrations were as follows: Old Tuberculin, 1:60 to 1:80; Water Extract, 1:5; Broth Filtrate, 1:20. The dilutions were made by taking up the required amounts of plasma and tuberculin in separate, sterile tuberculin syringes, adding them together in a sterile glass dish and mixing thoroughly by drawing the mixture into a syringe and expelling it into the dish several times. Dilutions of standard concentrated broth control for O.T. were prepared in the same manner. This broth control is merely glycerinated broth, such as that in which the bacilli are grown in the production of tuberculin, concentrated to the same degree as is O.T.

We now had washed cells from an allergic and a normal animal, and plasma from each animal as well. To part of the plasma from each

animal had been added a definite, and identical amount of tuberculin (in most of the experiments O.T. was used), and to another part the same amount of the concentrated broth control for O.T.; to part of the plasma nothing was added. It was now possible to place either normal or allergic washed cells in normal or allergic plasma with or without tuberculin, and we were able to proceed to set up the various combinations which we wished to study (see Table I). Each culture was made by taking up a fragment of washed buffy coat or splenic tissue in a capillary pipette, placing it in the centre of a sterile, square cover-slip, drawing off the excess of fluid and placing a small drop of plasma, plasma-tuberculin or plasma-control mixture over it. The cover-slip was then inverted over a slide on which there was an elevated ring of vaseline. It was pressed gently until an air-tight connection was made with the vaseline ring, and the culture was then placed in a thermostat kept at body temperature. The contact with the tissue ordinarily caused prompt clotting of the drop of heparinized plasma and migration was very soon under way. In each experiment from fifty to one hundred separate cultures were made. The cultures were examined from time to time over a period of several days and records were kept of the degree of migration and the viability of the cells in each separate culture. When we desired to preserve a series the cover-slips were removed and Zenker-formol was carefully dropped upon the cultures from a pipette. After five minutes' fixation the cover-slips with the adherent cultures were gently washed in 50–70 per cent alcohol and left for twenty-four hours in 80 per cent alcohol. The mercurial precipitate was then removed by immersion in an alcoholic solution of iodine followed by 5 per cent sodium hyposulphite, and each entire culture was stained with Harris' haemotoxylin, cleared in xylol and mounted in balsam.

EXPERIMENTAL RESULTS

In our first experiments the concentration of tuberculin (O.T.) was too strong, and all of the cells exposed to it, whether normal, or allergic, were damaged or killed. It is doubtful whether the damage to the normal cells in these early experiments was produced by tuberculoprotein itself. Subsequent experiments, in which the standard broth control for O.T. was used, showed that normal cells were damaged and killed by the broth control in concentrations in which tuberculin

affected them. Since both O.T. and the broth control contain large amounts of glycerin, it may be that the cells were damaged by that ingredient. We have made no attempt to analyze the cause of the damage to normal cells produced by high concentrations of tuberculin or the control solution, for with proper dilutions of O.T., and also with water extract and broth filtrate tuberculins, it was easy to show that normal cells would thrive in contact with amounts of tuberculoprotein which would kill outright the cells from the allergic body.

The damage done to allergic cells by tuberculoprotein is marked and easy to observe. It is evidenced by a decided inhibition of migration of the allergic cells from the explant into the surrounding tuberculin-containing plasma and by the fact that the relatively few cells which do wander out die in a few hours in contrast to the swarming migration of normal cells into the same medium, most of which remain alive and multiply for several days or more. It should be emphasized that the method of tissue culture is not an absolutely quantitative one by any means. In any large series of cultures made at the same time under the same conditions there will almost always be some unexplainable variations in the degree of migration and survival of individual cultures, and such variations were, of course, encountered in the present experiments. However, having been fully aware at the outset of the limitations of quantitative tissue culture observations, we were prepared to accept as positive evidence only very marked and highly consistent differences in the behavior of the cells under the different conditions to which they were exposed. The results of the experiments, which comprise nearly two thousand individual cultures, make it clear beyond any doubt that the washed blood or splenic cells from an allergic animal are hypersusceptible to tuberculin and are readily damaged and killed by amounts of Old Tuberculin, Water Extract or Broth Filtrate that do not harm the cells of the normal, non-allergic body.[2] It is

[2] Aronson has recently confirmed our preliminary report (8) of this phenomenon (*Jour. Exp. Med.*, Sept. 1931). Fischer (*Zeit. für Immunitätsforsch.*, 1928, lvi, 24) and Juhasz-Schäffer (*ibid.*, p. 377) claimed that tuberculin does not damage allergic cells *in vitro*, but the former used cultures which had been retransplanted through ten generations outside the allergic body, and both used dilutions of tuberculin far below the limits of concentration which both Aronson and ourselves found it necessary to use in order to affect the allergic cells.

furthermore clear that, after allergic hypersensitivity is established, the circulating plasma of the allergic body is not necessary for the toxic action of tuberculin, for the washed allergic cells are killed by it even when suspended in the plasma of a normal animal. Finally, this very sensitive method of study of free cells has failed to yield any convincing support for the possibility that, in tuberculin allergy, free antibody, capable of acting upon the foreign protein to produce a noxious substance, circulates in the blood in appreciable amount as it does in the case of Arthus phenomenon allergy. It is true that in certain cases the combination of allergic plasma and tuberculin seemed to be a somewhat less favorable medium for the normal cells than the combination of normal plasma and tuberculin, and this when the allergic plasma alone exerted none of the untoward effect upon the normal cells which is occasionally observed when the cells of one animal are grown in the plasma of another. It must remain possible that these may have been instances in which a barely detectable amount of antibody was actually present in the plasma of the particular allergic animals used in the experiments. Such irregular observations recall the occasional suggestively positive tuberculin reactions which are encountered when a mixture of tuberculin and plasma from an allergic animal is injected into the skin of a normal animal. In neither case, however, are the effects constant enough or pronounced enough to be of more than suggestive significance as an indication of the possible presence of a detectable amount of antibody in the plasma of some allergic animals. In no case was the inhibition of migration and survival of normal cells in the mixture of allergic plasma and tuberculin remotely comparable to the damage suffered by the allergic cells of the same series.

The protocol (table I) will serve as characteristic of the type of experiment carried out in the present work. Figures 1 to 10 are representative cultures fixed and stained at the end of twenty-four and forty-eight hours.

It is interesting that the polymorphonuclear and the monocyte-clasmatocyte cell types are apparently more susceptible to the action of tuberculin than are the fixed cells of the connective tissue. Thus, in cultures of splenic tissue from the allergic body the migration of free wandering cells is greatly inhibited by the presence of tuberculin and

the few migrating cells are rapidly killed, but if such cultures are kept for four or five days, there often appears a sprouting growth of connective-tissue cells which radiate from the explant and are not appre-

TABLE I

NUMBER OF CULTURES	WASHED CELLS FROM	GROWN IN PLASMA FROM	O.T. TUBERCULIN ADDED AT START	BROTH CONTROL ADDED AT START	MIGRATION AND GROWTH	CONDITION OF CELLS
10	Allergic animal	Allergic animal	1:60*		Very slight	Most dead within 48 hours
10	Allergic animal	Normal animal	1:60		Very slight	Most dead within 48 hours
10	Normal animal	Allergic animal	1:60		Very good	Very good during 4 days
10	Normal animal	Normal animal	1:60		Very good	Very good during 4 days
10	Allergic animal	Allergic animal		1:60*	Very good	Very good during 4 days
10	Allergic animal	Normal animal		1:60	Very good	Very good during 4 days
10	Normal animal	Allergic animal		1:60	Very good	Very good during 4 days
10	Normal animal	Normal animal		1:60	Very good	Very good during 4 days
5	Allergic animal	Allergic animal			Very good	Very good during 4 days
5	Allergic animal	Normal animal			Very good	Very good during 4 days
5	Normal animal	Allergic animal			Very good	Very good during 4 days
5	Normal animal	Normal animal			Very good	Very good during 4 days

* One-tenth cubic centimeter of these mixtures of allergic plasma and tuberculin and of allergic plasma and broth control were each injected intracutaneously into an allergic and a normal guinea-pig. At the end of 24 hours there was a definite reaction in the allergic pig at the site of the tuberculin-plasma mixture. It was 1.5 cm. in diameter, red, elevated and indurated. There was no reaction in the normal animal; nor did the broth control-plasma mixture cause any reaction in either animal.

ciably damaged as they grow into the tuberculin-plasma. It is true that in the presence of tuberculin the growth of connective tissue from explants of normal tissue is ordinarily more abundant than it is from allergic explants, so that the tuberculin in the concentrations used

does definitely damage the fixed connective-tissue cells of the allergic body; but it is also clear that, in concentrations of tuberculin which kill outright the blood cells and the wandering cells of the connective tissue, the fixed connective-tissue cells are less damaged and may even survive. In a number of experiments it seemed that the lymphocytes of the allergic body were also less susceptible to tuberculin than were the monocytes and polymorphonuclear cells, but we have not definitely decided that point.

DISCUSSION

It is clear from these experiments that the isolated cells of the allergic body are hypersensitive to tuberculin and that antibody, even if present in small amounts in the circulating plasma, is not necessary for the immediate damage, for the washed cells are damaged by tuberculin even when suspended in the plasma of a normal animal. In what the heightened susceptibility of the allergic cells consists we cannot say. It is conceivable, of course, that during the establishment of allergy the cells themselves have undergone some internal alteration which renders them susceptible to the action of tuberculoprotein, but it is much more probable that the change consists in the intimate attachment of antibody to the cells comparable to the fixation of antibody to smooth muscle cells, which is now generally believed to underlie the condition of anaphylaxis. In contrast to anaphylaxis, however, we have not been able, even by the sensitive method of tissue culture, to demonstrate convincingly the existence of appreciable amounts of antibody in the plasma of the tuberculous allergic body, although suggestive evidence of the presence of small amounts was occasionally obtained. This is in agreement with the generally unsuccessful attempts to transfer tuberculin allergy passively. It is, however, possible, and indeed highly probable, that minute amounts of antibody do circulate in the blood stream of the allergic body, for all the evidence that we possess indicates that antibody formation is not a common property of all cells. It is highly unlikely that all of the very different types of parenchymatous cells which are hypersensitive in the allergic body manufacture within themselves the antibody which renders them sensitive. A specialized group of cells, the evidence pointing suggestively to the macrophage

("reticulo-endothelial") system, is in all probability responsible for the formation of antibody; and if this be true, it is obvious that, since all tissues of the allergic body are hypersensitive, in order for antibody to become attached to distant cells it must travel to them by way of the blood stream. The chief fact of importance in the present study is that in the analysis of the mechanism of allergy it has been shown for the first time that just as the surplus of antibody in the blood in anaphylaxis is not necessary for the production of anaphylactic contraction of smooth muscle, but only that portion of antibody which is bound directly to the muscle cells, so in tuberculin allergy circulating antibody is not immediately necessary for the allergic damage which occurs in the presence of the antigen. If an antibody is involved at all, and it almost certainly is, it is only the portion bound directly to the tissue cells which is necessary for the occurrence of the local, allergic tissue reaction.

CONCLUSIONS

The washed cells of the allergic, tuberculous body have been shown to retain their hypersensitivity to tuberculin when isolated from the body in tissue cultures. It is therefore clear that neither circulatory, nervous nor other mechanisms dependent upon the intact body are necessary for the production of allergic damage.

Cellular injury and necrosis associated with allergy in tuberculosis result from a change in the individual fixed tissue and blood cells, which renders them hypersensitive to the protein of the tubercle bacillus. This change, in all probability, consists in the intimate attachment of antibody to the cells. Free, circulating antibody is not necessary for the production of the immediate, local injurious effects of allergy in tuberculosis.

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EXPLANATION OF FIGURES

See table I and text for more complete explanation.

Figures 1 through 8 are all the same magnification.

FIG. 1. Washed normal cells, allergic plasma, tuberculin 1:60, 24 hours.

FIG. 2. Washed allergic cells, allergic plasma, tuberculin 1:60, 24 hours.

FIG. 3. Washed normal cells, allergic plasma, tuberculin 1:60, 48 hours.

FIG. 4. Washed allergic cells, allergic plasma, tuberculin 1:60, 48 hours.

These first four figures show the swarming migration of normal cells into the plasma-tuberculin medium. The combination of allergic plasma with tuberculin has not damaged the normal cells. In contrast the allergic cells show a very much restricted migration and most of the migrated cells are dead at 24 hours. The small dots in each case are the cells which have migrated from the explant which appears as the central black area.

FIG. 5. Washed normal cells, normal plasma, tuberculin 1:60, 24 hours.

FIG. 6. Washed allergic cells, normal plasma, tuberculin 1:60, 24 hours.

FIG. 7. Washed normal cells, normal plasma, tuberculin 1:60, 48 hours.

FIG. 8. Washed allergic cells, normal plasma, tuberculin 1:60, 48 hours.

Figures 5 to 8 show that washed cells of the allergic body are killed and their migration inhibited by tuberculin even when surrounded by normal plasma. This makes it evident that the plasma of the allergic body is not necessary for the allergic damage.

FIG. 9. High-power magnification of migrated cells in fig. 3. At 48 hours the cells from the normal body are entirely normal in a medium of allergic plasma + tuberculin 1:60.

FIG. 10. Same magnification as fig. 9. The cells are from the migration zone of fig. 8. At 48 hours the cells from the allergic body are dead (note pyknosis and karyorhexis) in a medium of normal plasma + tuberculin 1:60.

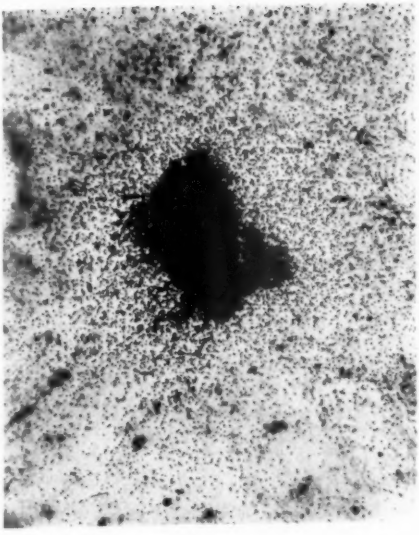

FIG. 1

FIG. 2

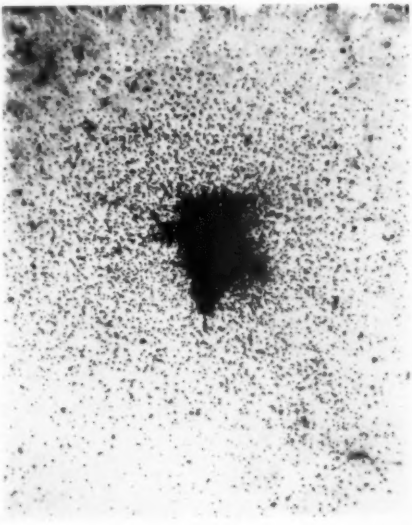

FIG. 3

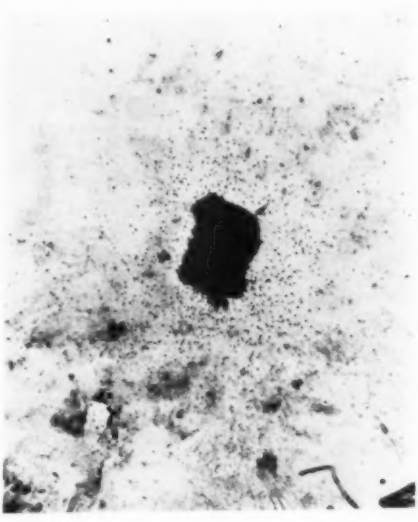

FIG. 4

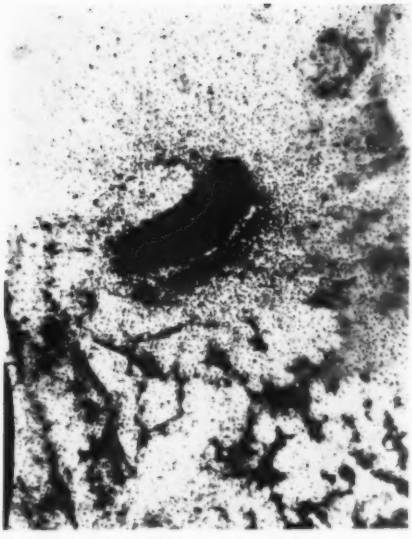

FIG. 5

FIG. 6

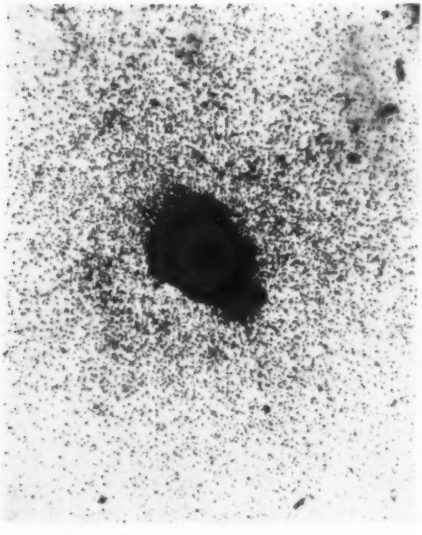

FIG. 7

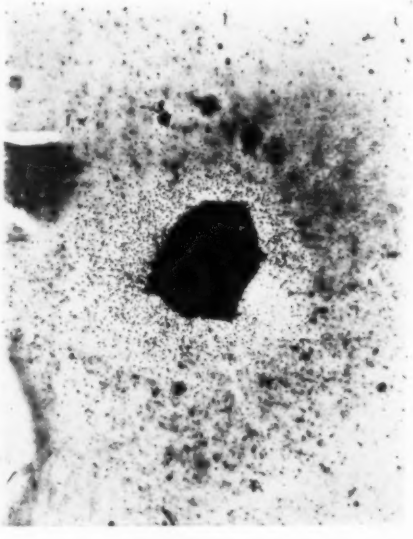

FIG. 8

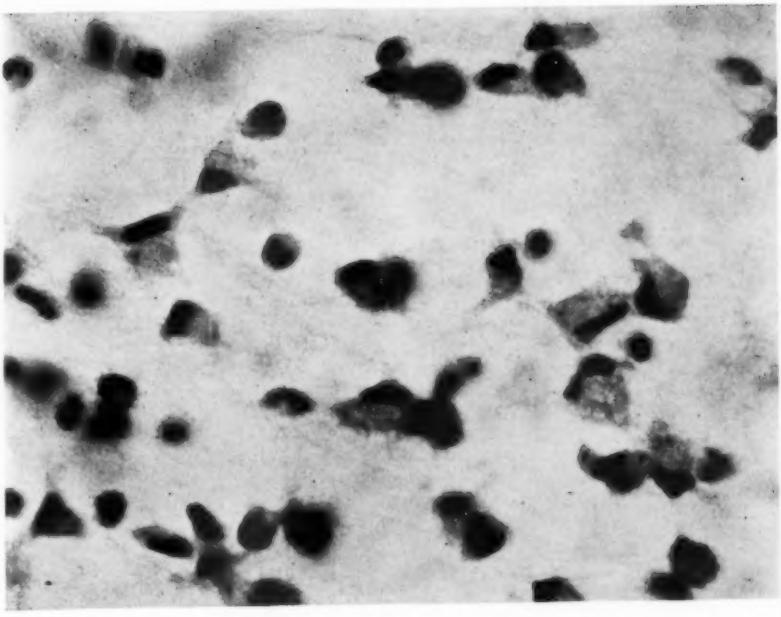

FIG. 9

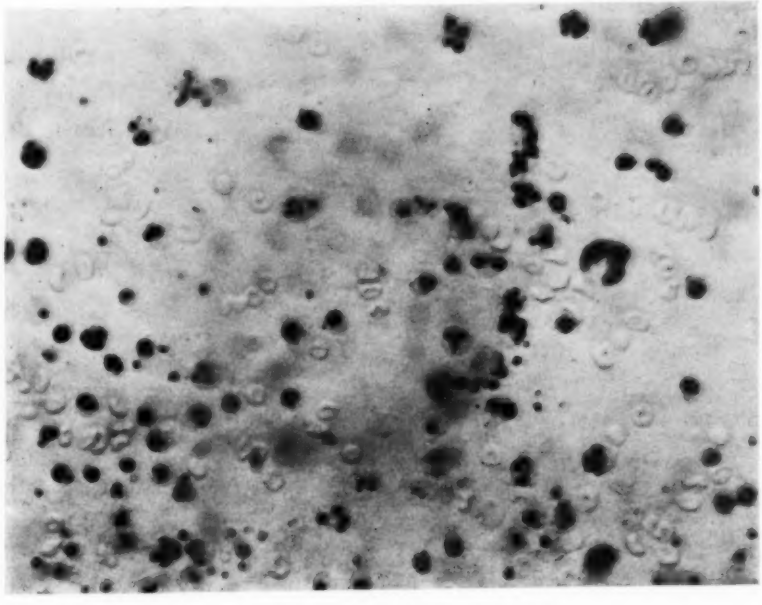

FIG. 10

BOOK REVIEWS

Diet in Disease. By GEO. A. HARROP, JR., M.D., Assoc. Prof. of Medicine, Johns Hopkins University. With eighty tables, sample diets and food lists. Pp. 404. (*P. Blakiston's Sons & Co., Inc., Philadelphia, 1930*).

During the past few years the number of books dealing with Dietetics has been quite large. Most of them have found a restricted reception either because they have been so large and detailed as to make them of use only to the research worker, or because they have been somewhat fragmentary and of value only to the beginner in medicine.

The volume is divided into three parts: the first considers the requirements of nutrition, the second, the elements of diet, and the third, which forms the major part of the book, the dietary treatment of diseases. It is full of valuable information as to the proper foods, their composition and their selection and preparation in specific diseases. Best of all, it is readable and contains all the essential tables of food values which one might need in arranging a diet. These are found very conveniently scattered throughout the book under the discussions to which they belong.

The author has shown a definite honesty of thought and sanity of reasoning in discussing the many problems which arise in considering the value of certain types of diet for various morbid conditions. Especially is this true in his handling of the often debated question of the difference between red and white meats in the treatment of chronic nephritis. Likewise the value of restriction of sodium chloride in cases of hypertension is discussed in a thoroughly modern and up to date manner.

The format of the book is very good. It is of convenient size and has a readable text. The list of references, placed at the end of each section, should be of great value to any reader who seeks more detailed information than can be presented in a volume of this size.

E. L.

An Introduction to Malariology. By MARK F. BOYD. 437 pages. (*Harvard University Press, Cambridge, Mass., 1930.*)

As the author puts it, "the aim of this treatise is a presentation of the technical knowledge necessary to make an epidemiological diagnosis of a malaria problem, and not an exposition of methods for its eradication or control."

It presents a most valuable and exhaustive summary of the principles and methods of Malaria Surveys and of Anopheline Surveys, based upon extensive personal experience in the field and a wide acquaintance with the world literature of the subject. This volume is such an outstanding contribution that one is led

to hope that Doctor Boyd will some day undertake the preparation of an equally satisfactory handbook on the subject of malaria control.

F. M. R.

An Introduction to Pharmacology and Therapeutics. By J. A. GUNN. 2d edition. viii, 233 pp. $1.50. (*Humphrey Milford, Oxford University Press, 1931.*)

The second edition of this serviceable little compendium contains a new chapter on the action of drugs on the respiratory system, with slight additions to existing chapters. Needful brevity is achieved by careful selection and arrangement of topics rather than by compression—an excellent feature from the standpoint of the busy student.

W. G. S.

The Treatment of Chronic Deafness by the Electrophonoïde Method of Zünd-Burguet. By GEORGE C. CATHCART. 2d edition. xiii, 111 pp. $1.50. (*Humphrey Milford, Oxford University Press, 1931.*)

Opinion on the merits of the Zünd-Burguet electrophonoïde method for treating deafness is still very much in the controversial stage as evidenced by the author's preface to the second edition of this book. Dr. Cathcart sets forth his experience in the use of this method of auditory re-education in nine chapters of which the last four are naturally the most important, because in them are outlined the method, the value, and the results, in tabulated form, of 665 cases occurring in his own practice.

W. G. S.

Surgery at the New York Hospital One Hundred Years Ago. By EUGENE H. POOL and FRANK J. MCGOWAN. xi, 188 pp. $1.50. (*New York, Paul B. Hoeber, 1930.*)

This informing little volume is really a tabulation in extended form of case records in surgery as practiced in the New York Hospital between the years 1808 and 1833.

On the side of technique it is mainly of antiquarian interest, but very readable considering the types of operations undertaken in a period when there were few aids to diagnosis, no thermometer, no stethoscope, no auscultation, and no nurses to assist in treatment. One of the cases cited, giving an account of an occurrence of spontaneous dislocation of the crystalline lens, will interest ophthalmologists. Genealogical angles are afforded by full names, dates, and occupations of patients treated. Facsimiles and portraits of eminent physicians and surgeons of the time are abundant. Biographic letterpress descriptions accompanying the portraits will be welcomed as pertinent and time-saving.

W. G. S.

Allergie des Lebensalters; die bösartigen Geschwülste. By CLEMENS PIRQUET. Price 23 marks. (*Publisher, George Thieme, Leipzig, 1930.*)

It was Pirquet's original plan to construct, from an analysis of mortality and morbidity statistics, a general atlas of the age distribution of the different diseases which afflict mankind. This was not carried to completion before his death, and the present posthumous work of one hundred and seventy pages, which are for the most part occupied by tables, charts and curves, represents only an analysis of certain English mortality statistics relating to malignant tumors. One can find here a curve representing the frequency of occurrence of malignant tumors in each separate organ, in either sex and at every age. Nothing startlingly new is brought out by this laborious analysis, but it will be of use to anyone who wishes to know the relative frequency with which primary malignant tumors arise in any particular organ, and the relation of susceptibility to age and sex. The conclusions are no more or less accurate than the ability of the English physician to reach a correct diagnosis, for this is not a survey of cases carefully checked by autopsy. The source of the material obviously permitted no attempt to separate the tumors into different histological types, nor is there any separation of carcinomata from sarcomata.

The title of the book is a decidedly unfortunate one, and can only serve to increase the difficulty of using the term "allergy" in a sense which will be generally understood. At present, although there are certain differences in the specific phenomena which are included in the term by different writers, "allergy" has come to be quite generally used to designate the condition of hypersensitivity which is developed when foreign protein, whether bacterial or non-bacterial, finds its way parenterally into the animal body. To extend the term to include the condition of susceptibility to malignant tumors, which appears at different periods of life, is perfectly justifiable from a strictly etymological standpoint; but etymology is the very poorest measure of correctness of usage, and it is safe to say that the introduction of this complication will not be particularly relished by those who are already beset by the difficulties surrounding this attractive term. It may be felt that if any man in the world had the right to use the term "allergy" in any sense he chose that man was Pirquet, since it was he who created the word some thirty years ago. But a word once given to the world and accepted by it ceases to be the property of the donor, and in the present case it is to be hoped that the authority of Pirquet will not serve to stimulate a fresh outburst of lax application of the term; else an excellent and a potentially very useful word, which is now approaching stabilization in usage, will be degenerated into a condition of complete incomprehensibility through being applied, for high-sounding purposes, to every conceivable sort of physiological or pathological *change* which occurs in the animal body.

A. R. R.